10/528413

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DESCRIPTION

ANTITUSSIVES

TECHNICAL FIELD

The present invention relates to antitussives, in particular to antitussives possessing a strong antitussive effect and a compound used in these antitussives.

BACKGROUND ART

Antitussives are used in the treatment of coughing resulting from a variety of respiratory illnesses such as a cold syndrome, bronchitis, and pneumonia and are classified either as a central antitussive, which affects the cough center of the brain, or as a peripheral antitussive, which supposedly blocks the cough stimulus sent by the afferent pathway or the stimulus sent from the cough center by the efferent pathway at the periphery (respiratory tract, lungs, respiratory muscles, or the like). However, most medications presently used are central antitussive.

Central antitussives are further classified as either narcotic or nonnarcotic. As narcotic antitussives, codeine phosphate, dihydrocodeine phosphate, and the like are known, and as nonnarcotic antitussives, compounds such as tipepidine hibenzate, dextromethorphan hydrobromide, and the like are known.

Narcotic antitussives possess a strong antitussive effect, but produce side effects such as constipation, nausea and vomiting, headaches, and drowsiness, and cause problems such as resistance and dependency when administered on a daily basis. Even though nonnarcotic antitussives are known not to cause resistance and dependency and to produce only mild side effects, influence to parts of the body other than the cough center cannot be avoided and side effects such as drowsiness, dizziness, and headaches may occur. Also, the antitussive effect of nonnarcotic antitussives is inadequate when

compared with narcotic antitussives.

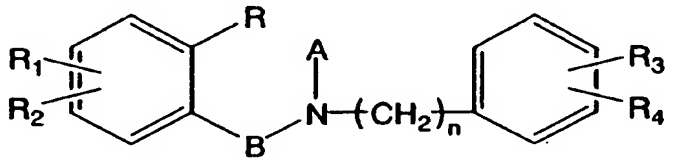
Therefore, a substance possessing a strong peripheral antitussive effect while exhibiting almost no central side effects has been desired. However, there have been nearly no reports concerning such a substance.

The object of the present invention is to provide a compound possessing an antitussive effect, in particular, a novel compound possessing a peripheral antitussive effect.

DISCLOSURE OF THE INVENTION

After synthesizing many compounds in search of a compound possessing an excellent antitussive effect in order to overcome the above problems, the present inventors have found that compounds with a certain structure possess an antitussive effect, and some of these compounds possess a peripheral antitussive effect without central side effects, thereby completing the present invention.

Specifically, the present invention provides an antitussive comprising the compound of the following formula (I) or the pharmacologically acceptable salt thereof as an active component.



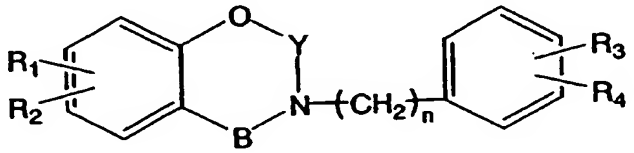
(I)

① ②

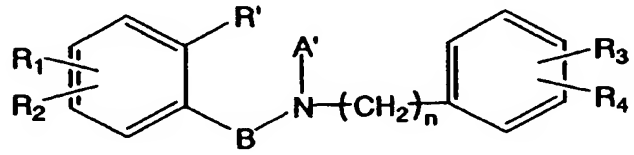
wherein A represents an alkoxycarbonylalkyl group, carboxylalkyl group, pyridylalkyl group, pyridine oxid-yl alkyl group, quinolylalkyl group, indolylalkyl group, pyrrolidylalkyl group, furylalkyl group, thienylalkyl group, pyrrolylalkyl group, imidazolylalkyl group, pyrazolylalkyl group, thiazolylalkyl group, aminocarbonylalkyl

group, cyanoalkyl group, or carboxylbenzyl group; R represents a protected or unprotected hydroxyl group or may combine with A to form a six or seven member ring comprising an oxygen atom; B represents a carbonyl group or sulfonyl group; R_1 and R_2 individually represent a hydrogen atom, alkoxy group, benzyloxy group, halogen atom, alkyl group, hydroxyl group, alkoxycarbonylalkyloxy group, or carboxylalkyloxy group; R_3 and R_4 individually represent a hydrogen atom, alkoxy group, benzyloxy group, halogen atom, alkyl group, hydroxyl group, alkoxycarbonylalkyloxy group, carboxylalkyloxy group, cyanoalkyloxy group, aminosulfonyl group, hydroxyalkyloxy group, aminocarbonylalkyloxy group, or may join to form an alkylene dioxy group; and n is 1 or 2.

Furthermore, the present invention provides a novel compound shown by the following formula (IA) or (IB),



(IA)



(IB)

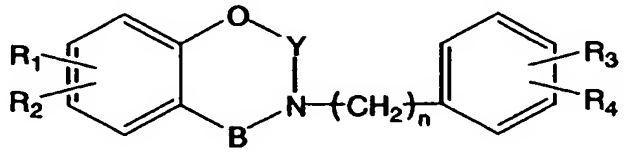
wherein Y represents a methylene group, ethylene group, carbonyl group, or methylene carbonyl group; R' represents a protected or unprotected hydroxyl group; A' represents an alkoxycarbonylalkyl group, carboxyalkyl group, pyridylalkyl group, pyridineoxid-yl alkyl group, quinolylalkyl group, indolylalkyl group, pyrrolidylalkyl group, furylalkyl group, thienylalkyl group, pyrrolylalkyl group, imidazolylalkyl group, pyrazolylalkyl group, thiazolylalkyl group, aminocarbonylalkyl group, cyanoalkyl group, or carboxyl

benzyl group; and B, R_1, R_2, R_3, R_4, and n are the same as defined above.

BEST MODE FOR CARRYING OUT THE INVENTION

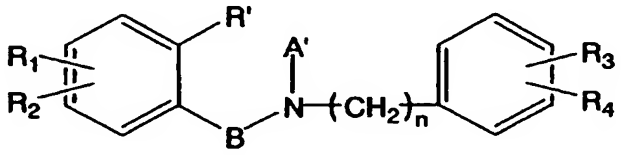
Even though the compound shown by the formula (I) of the present invention includes some known compounds, most of the compounds are novel compounds.

The novel compounds of the above compound (I) can be largely divided into the two following groups represented by the above formulas (IA) and (IB).



(IA)

wherein B, R_1, R_2, R_3, R_4, Y, and n are the same as defined above.



(IB)

wherein A', B, R', R_1, R_2, R_3, R_4, and n are the same as defined above.

In the above formulas (IA) and (IB), as the alkoxy group, a substituted or unsubstituted lower alkoxy group having 1-4 carbon atoms such as an ethoxy group and methoxy group is preferable, and as the alkyl group, a substituted or unsubstituted lower alkyl group having 1-4 carbon atoms such as a methyl group and ethyl group are preferable. Of the substituents, a methyl group and halogen atoms such as a fluoro atom and chloro atom are preferable. As the alkylene dioxy group, a methylene dioxy group, ethylene dioxy group, propylene dioxy group, and the like are preferable.

As the alkoxy groups and alkyl groups in the alkoxycarbonylalkyl group, carboxyalkyl group, pyridylalkyl group, pyridineoxide-ylalkyl group, or

aminocarbonylalkyl group, lower alkoxy groups and lower alkyl groups having 1-4 carbon atoms are preferable.

As the protective group for protecting the hydroxyl group, a benzyl group, lower alkyl group, acetyl group, and the like can be given.

The compounds of the above formulas (IA) and (IB) can be synthesized in accordance with the following reaction formulas, for example.

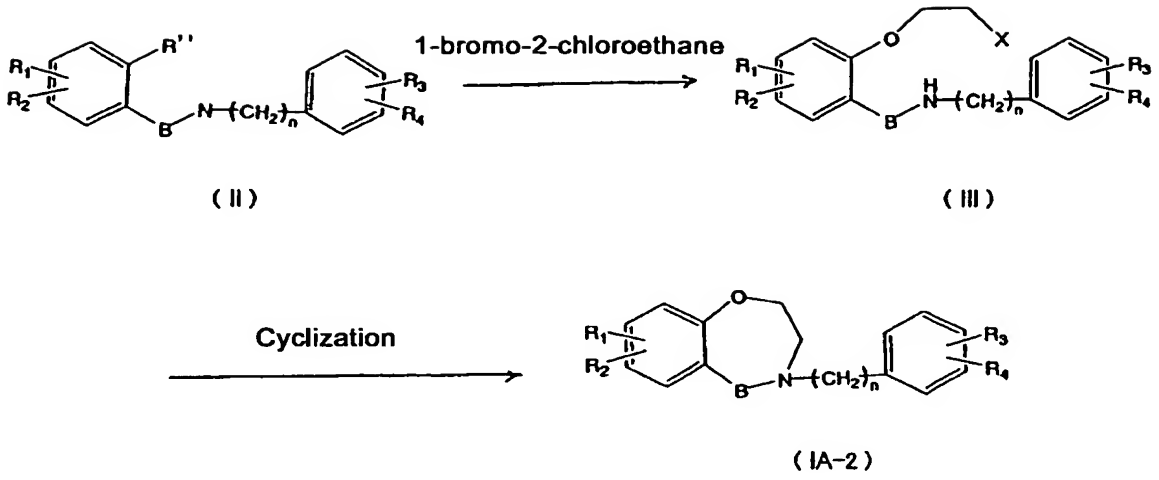
(a) The compound (IA-1), a compound having a methylene group for Y in the formula (IA), can be obtained by, for example, reacting the compound of the following formula (II) with formaldehyde or its derivative such as paraformaldehyde and dimethoxymethane in accordance with the following reaction formula.

(II)　　(IA-1)

wherein R" represents a hydroxyl group and B, R_1, R_2, R_3, R_4, and n are the same as defined above.

In the above reaction, the compound (II) is cyclized by reacting with formaldehyde or its derivative at a molar ratio of 1-100:1 either in the presence or absence of a solvent such as chloroform, dichloromethane, toluene, DMF, DMSO, and 1,4-dioxane at a temperature of -50°C to 100°C using an acid such as paratoluenesulfonic acid and sulfuric acid.

(b) The compound (IA-2), a compound having an ethylene group for Y in the formula (IA), can be obtained by, for example, reacting the compound of the following formula (II) with 1-bromo-2-chloroethane or the like to obtain the compound of the formula (III), followed by cyclization in accordance with the following reaction formula.



(II)

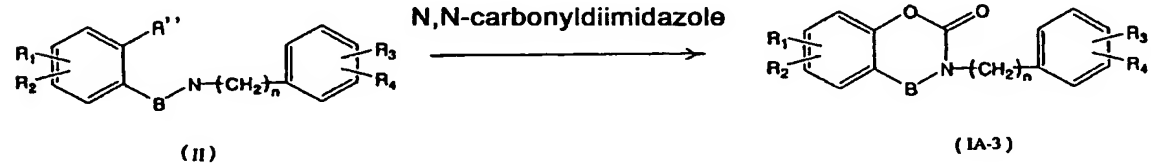
(III)

(IA-2)

wherein X represents a halogen atom and B, R", R_1, R_2, R_3, R_4, and n are the same as defined above.

In the above reaction, a compound such as 1-bromo-2-chloroethane and the compound (II) at a molar ratio of 1-10:1 are reacted in the presence of a solvent such as acetone, DMF, DMSO, and toluene at a temperature of -50°C to 150°C, followed by cyclization at a temperature of -50°C to 150°C using a base such as potassium carbonate, sodium hydroxide, and sodium hydride.

(c) The compound (IA-3), a compound having a carbonyl group for Y in the formula (IA), can be obtained by, for example, reacting the compound of the following formula (II) with N,N-carbonyldiimidazole and the like in accordance with the following reaction formula.



(II)

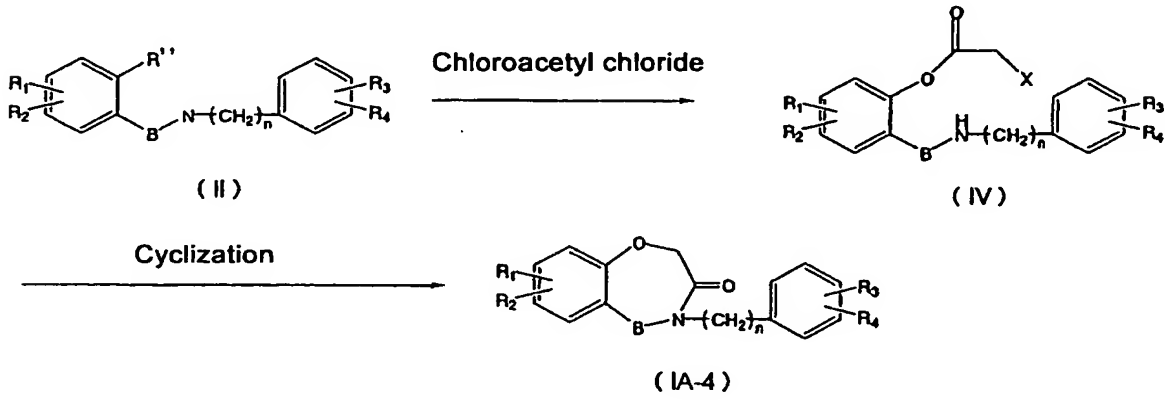
(IA-3)

wherein B, R", R_1, R_2, R_3, R_4, X, and n are the same as defined above.

In the above reaction, the compound (II) is cyclized by the reaction with a compound such as N,N-carbonyldiimidazole at a molar ratio of 1-10:1 either in the presence or absence of a solvent such as chloroform, dichloromethane, toluene, DMF, and

DMSO at a temperature of -50°C to 150°C.

(d) The compound (IA-4), a compound having a ethylenecarbonyl (-CH_2CO-) group for Y in the formula (IA), can be obtained by, for example, reacting the compound of the following formula (II) with chloroacetyl chloride or the like to obtain the compound of the formula (IV), followed by cyclization in accordance with the following reaction formula.



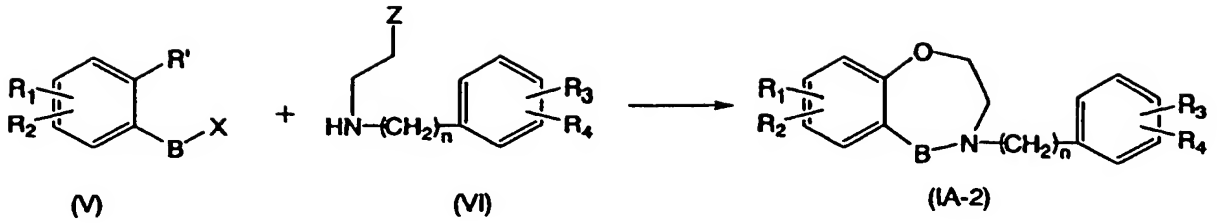
(II)　　(IV)

(IA-4)

wherein R" represents a hydroxyl group and B, R_1, R_2, R_3, R_4, and n are the same as defined above.

In the above reaction, a compound such as chloroacetyl chloride and the compound (II) at a molar ratio of 1-10:1 are reacted either in the presence or absence of a solvent such as chloroform, dichloromethane, toluene, DMF, and DMSO at a temperature of -50°C to 150°C, followed by cyclization at a temperature of 0°C to 100°C using a base such as potassium carbonate and sodium hydride.

(e) The compound (IA-2), a compound having an ethylene group for Y in the formula (IA), can be obtained by, for example, reacting the compound of the following formula (V) or a reactive derivative thereof with a disubstituted amine compound of the formula (VI), followed by cyclization in accordance with the following reaction formula.

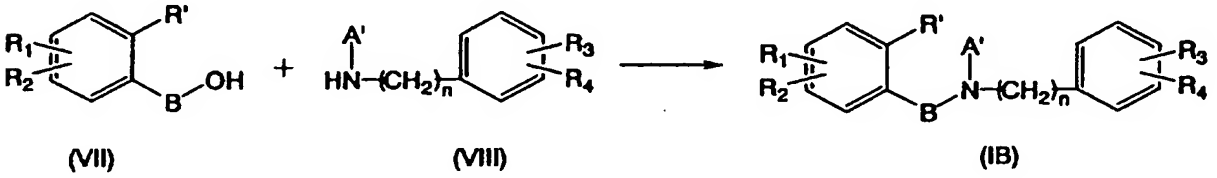


(V) (VI) (IA-2)

wherein Z represents a halogen atom and B, R', R_1, R_2, R_3, R_4, X, and n are the same as defined above.

In the above reaction, disubstituted amine (VI) and the compound (V) at a molar ratio of 1-10:1 are reacted either in the presence or absence of a solvent such as ethyl acetate at a temperature of -50°C to 150°C in the presence of a base such as DBU.

(f) The compound (IB) can be obtained by reacting the compound of the formula (VII) or the reactive derivative thereof with the disubstituted amine compound of the formula (VIII), and if necessary, transforming the substituent.



(VII) (VIII) (IB)

wherein A', B, R', R_1, R_2, R_3, R_4, and n are the same as defined above.

In the above reaction, disubstituted amine (VIII) and the compound (VII) at a molar ratio of 1-10:1 are condensed either in the presence or absence of a solvent such as chloroform, dichloromethane, toluene, and DMF at a temperature of -50°C to 150°C.

The compounds obtained by the above methods are purified by a common purification process such as recrystallization and various types of chromatography, and if necessary converted into salts, to be used as an antitussive.

The medication form of the antitussive of the present invention containing the compound of formula (I) may be suitably chosen from any common form without any

limitations. As examples of the form of medication, orally administered forms such as tablet, capsule, granules, subtle granules, powder, and liquid or non-orally administered forms such as injection, suppository, and respiratory tonic can be given.

The antitussive of the present invention is preferably administered orally. Even though the amount of the compound (I) to be administered differs depending on the patient's age, sex, and weight, and degree of the ailment, for an adult, the compound is usually administered in an amount in a range of 1-100 mg per day and preferably administered several times a day.

A solid-type oral preparation can be manufactured by a known method using the compound of the present invention as is or combined with a vehicle such as a starch, lactose, white sugar, mannite, carboxymethylcellulose, corn starch, or inorganic salt. In addition to the above vehicle, binders, disintegrating agents, surfactants, lubricants, fluidity promoters, flavoring substances, coloring agents, and perfumes may be suitably selected and used.

As examples of the binder used in the preparation of the solid-type oral preparation, starch, dextrin, gum arabic, gelatin, hydroxypropyl starch, methyl cellulose, carboxymethylcellulose sodium, hydroxypropyl cellulose, crystal cellulose, ethyl cellulose, polyvinyl pyrrolidone, and macrogol can be given. As examples of the disintegrating agent, starch, hydroxypropyl starch, carboxymethylcellulose sodium, carboxymethylcellulose calcium, carboxymethylcellulose, and low substitution hydroxypropyl cellulose can be given. As examples of the surfactant, sodium lauryl sulfate, soybean lecithin, sucrose fatty acid ester, and polysorbate 80 can be given.

As examples of the lubricant, talc, wax, hydrogenated vegetable oil, sucrose fatty acid ester, magnesium stearate, calcium stearate, aluminum stearate, and polyethylene glycol can be given. As examples of the fluidity promoter, light anhydrous silicic acid, dried aluminum hydroxide gel, synthetic aluminium silicate, and magnesium silicate can be given.

Furthermore, the antitussive of the present invention can be administered as a liquid-type oral agent such as a suspension, emulsifier, syrup, and elixir. In these forms, a flavoring substance or coloring agent may be used.

On the other hand, the antitussive of the present invention may be used in the form of a non-oral agent. As the amount of the compound (I) to be administered in this form, even though the amount differs depending on the patient's age, sex, and weight, and degree of the ailment, for an adult, the compound is usually administered in an amount in a range of 1-300 mg per day preferably by an IV, IV drip infusion, hypodermic injection, or intramuscular injection.

In the preparation of the non-oral agent, the compound (I) can be diluted with an appropriate diluent. As the diluent, generally, distilled water for injection, physiological saline solution, glucose aqueous solution, vegetable oil for injection, sesame oil, peanut oil, soybean oil, corn oil, propylene glycol, and polyethylene glycol can be used. If necessary, a disinfectant, antiseptic agent, and stabilizer may be used in the non-oral agent.

To ensure storage stability, the injection preparation is charged into a vial and freeze dried using a common freeze drying method in order to remove water then stored in a freeze dried state and is restored to a liquid state before use. If necessary, an isotonic agent, stabilizer, antiseptic, soothing agent, and the like may be used in the injection preparation.

As examples of other non-oral agents, liniments such as externally applied liquid medications and ointments and suppositories for application in the rectum prepared in accordance with common methods can be given.

As explained above, the antitussive of the present invention can be broadly applied to the treatment of coughing accompanying respiratory ailments such as the cold syndrome, bronchitis, and pneumonia.

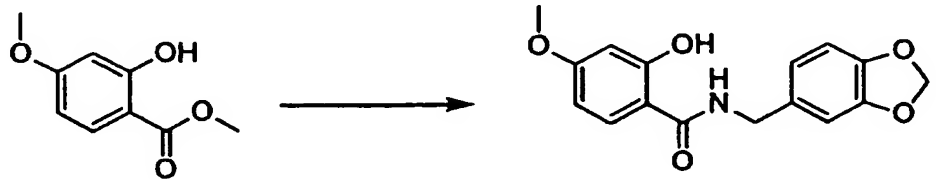
EXAMPLES

The present invention will be described in more detail by way of Preparation Examples and Test Examples which should not be construed as limiting the present invention.

Preparation Example 1

Synthesis of 2-hydroxy-4-methoxy-N-[3,4-(methylenedioxy)benzyl]benzamide

A mixture of 3.12 g (17.1 mmol) of methyl 4-methoxysalicylate and 4.3 ml (34.3 mmol) of piperonylamine was stirred for three hours at 150°C. The resulting crude product was purified by silica gel column chromatography (hexane : ethyl acetate = 4 : 1) to obtain 1.96 g (yield: 38%) of the title compound (BAK-G202).



BAK-G202

^{1}H-NMR($CDCl_3$)δ:

3.81 (s, 3H), 4.51 (d, J=5.6Hz, 2H), 5.96 (s, 2H), 6.31 (brs, 1H), 6.38 (dd, J=2.5, 8.9Hz, 1H), 6.75-6.85 (m, 3H), 7.23 (d, J=8.9Hz, 1H), 12.63 (s, 1H)

MS(EI)E/Z301(M^+)

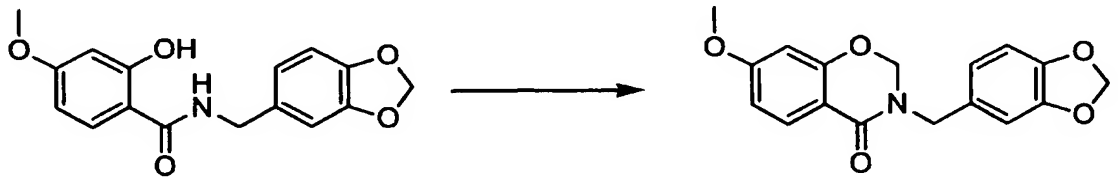
Preparation Example 2

Synthesis of

2,3-dihydro-7-methoxy-3-[3,4-(methylenedioxy)benzyl]-4H-1,3-benzoxazin-4-one

A mixture of 209.9 mg (0.697 mmol) of BAK-G202 obtained in Preparation Example 1, 105 mg (3.49 mmol) of paraformaldehyde, 132 mg (0.697 mmol) of

paratoluenesulfonic acid monohydrate, and 4 ml of dichloromethane was stirred at room temperature for two hours. A saturated aqueous solution of sodium hydrogencarbonate was added to the reaction solution, the mixture was extracted with dichloromethane, and the resulting organic layer was dried over anhydrous sodium sulfate. After concentration, the resulting crude product was purified by silica gel column chromatography (hexane : ethyl acetate = 2 : 1) to obtain 59.9 mg (yield: 27%) of the title compound (BAK-G203).



BAK-G202 BAK-G203

^{1}H-NMR($CDCl_3$)δ:

3.83 (s, 3H), 4.64 (s, 2H), 5.09 (s, 2H), 5.95 (s, 2H), 6.43 (d, J=2.4Hz, 1H), 6.67 (dd, J=2.4, 8.7Hz, 1H), 6.75-6.85 (m, 3H), 7.93 (d, J=8.7Hz, 1H)

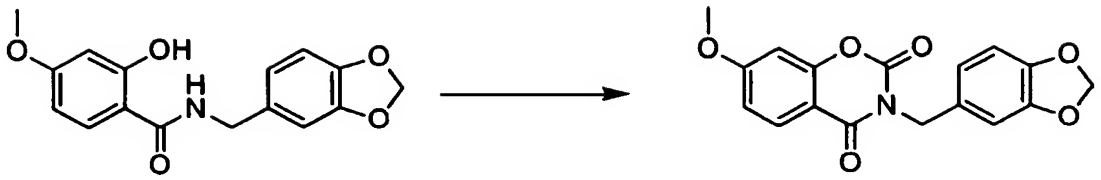
MS(EI)E/Z313(M^+)

Preparation Example 3

Synthesis of

7-methoxy-3-[3,4-(methylenedioxy)benzyl]-2H-1,3-benzoxazin-2,4(3H)-dione

A mixture of 221.7 mg (0.737 mmol) of BAK-G202 obtained in Preparation Example 1, 179 mg (1.10 mmol) of 1,1'-carbonyldiimidazole, and 4 ml of dichloromethane was stirred for one hour while cooling with ice. Water was added to the reaction solution, the mixture was extracted with dichloromethane, and the resulting organic layer was dried over anhydrous sodium sulfate. After concentration, the resulting crude product was purified by silica gel column chromatography (dichloromethane : hexane = 2 : 1) to obtain 202.6 mg (yield: 84%) of the title compound (BAK-G219).



BAK-G202 BAK-G219

^{1}H-NMR($CDCl_3$)δ:

3.89 (s, 3H), 5.08 (s, 2H), 5.92 (s, 2H), 6.68 (d, J=2.3Hz, 1H),

6.75 (d, J=8.5Hz, 1H), 6.88 (d, J=8.8, 2.3Hz, 1H), 7.00-7.05 (m, 2H),

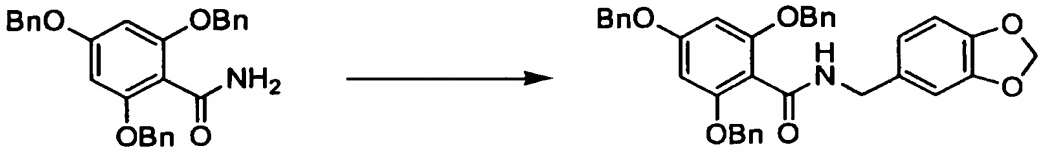
7.98 (d, J=8.8Hz, 1H)

MS(EI) E/Z327 (M^+)

Preparation Example 4

Synthesis of 2,4,6-tris(benzyloxy)-N-[3,4-(methylenedioxy)benzyl]benzamide

84 mg (2.1 mmol) of sodium hydride (60% oil) was added to a mixture of 460 mg (1.05 mmol) of 2,4,6-tri(benzyloxy)benzamid and 10 ml of toluene. The resulting mixture was stirred for 30 minutes at 100°C. 0.2 ml of piperonyl chloride was added to the reaction mixture and the mixture was further stirred for two hours at 100 °C. Water was added to the reaction solution, the mixture was extracted with ethyl acetate, and the resulting organic layer was dried over anhydrous sodium sulfate. After concentration, the resulting crude product was purified by silica gel column chromatography (hexane : ethyl acetate = 3 : 1) to obtain 256.2 mg (yield: 43%) of the title compound (BAK-G232-2).



BAK-G228 BAK-G232-2

^{1}H-NMR($CDCl_3$)δ:

4.49 (d, J=5.7Hz, 2H), 4.97 (s, 2H), 5.05 (s, 4H), 5.89 (s, 2H),

5.95 (t, J=5.7Hz, 1H), 6.23 (s, 2H), 6.54 (d, J=7.9Hz, 1H),

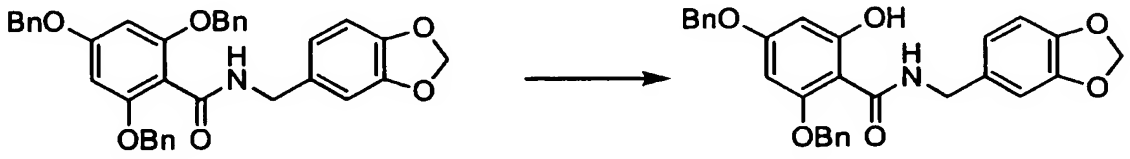
6.69 (dd, J=1.6, 7.9Hz, 1H), 6.77 (d,J =1.6Hz, 1H), 7.25-7.45 (m, 15H)

MS(EI)E/Z573(M^+)

Preparation Example 5

Synthesis of 2,4-bis(benzyloxy)-6-hydroxy-N-[3,4-(methylenedioxy)benzyl]benzamide

1 ml of concentrated hydrochloric acid was added to a mixture of 284 mg (0.495 mmol) of BAK-G232-2 obtained in Preparation Example 4 and 10 ml of 1,4-dioxane. The resulting mixture was stirred for 30 minutes at 80 °C. Water was added to the reaction solution, the mixture was extracted with ethyl acetate, and the resulting organic layer was dried over anhydrous sodium sulfate. After concentration, the resulting crude product was purified by silica gel column chromatography (hexane : ethyl acetate = 5 : 1) to obtain 143.1 mg (yield: 60%) of the title compound (BAK-G238).



BAK-G232-2 BAK-G238

^{1}H-NMR($CDCl_3$)δ:

4.34 (d, J=5.4Hz, 2H), 4.99 (s, 2H), 5.05 (s, 2H), 5.95 (s, 2H),

6.13 (d, J=2.3Hz, 1H), 6.24 (d, J=2.3Hz, 1H), 6.50-6.60 (m, 2H),

6.66 (d, J=7.8Hz, 1H), 7.25-7.45 (m, 10H), 8.37 (t, J=5.4Hz, 1H),

14.29 (s, 1H)

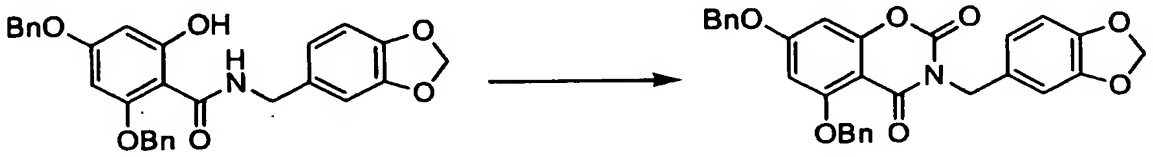
MS(EI) E/Z483 (M^+)

Preparation Example 6

Synthesis of

5,7-bis(benzyloxy)-3-[3,4-(methylenedioxy)benzyl]-2H-1,3-benzoxazin-2,4(3H)-dione

The title compound (BAK-G246) was obtained at a yield of 62% in the same manner as in Preparation Example 3.



BAK-G238 BAK-G246

^{1}H-NMR($CDCl_3$)δ:

5.06 (s, 4H), 5.22 (s, 2H), 5.91 (s, 2H), 6.37 (d, J=2.2Hz, 1H), 6.43 (d, J=2.2Hz, 1H), 6.74 (dd, J=0.9, 7.5Hz, 1H), 7.00-7.10 (m, 2H), 7.30-7.55 (m, 10H)

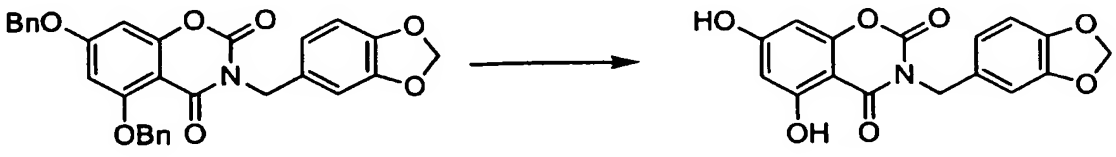
MS(EI)E/Z509(M^+)

Preparation Example 7

Synthesis of

5,7-dihydroxy-3-[3,4-(methylenedioxy)benzyl]-2H-1,3-benzoxazin-2,4(3H)-dione

A mixture of 45 mg (0.088 mmol) of BAK-G246 obtained in Preparation Example 6, 10 ml of ethyl acetate, and 5mg of 10% Pd-C was stirred for six hours under hydrogen atmosphere. After filtrating the reaction solution through celite, the filtrate was concentrated to obtain 26.8 mg (yield: 92%) of the title compound (BAK-G248).



BAK-G246 BAK-G248

^{1}H-NMR(acetone-d_6)δ:

5.02 (s, 2H), 5.97 (s, 2H), 6.24 (d, J=2.1Hz, 1H), 6.26 (d, J=2.1Hz, 1H),

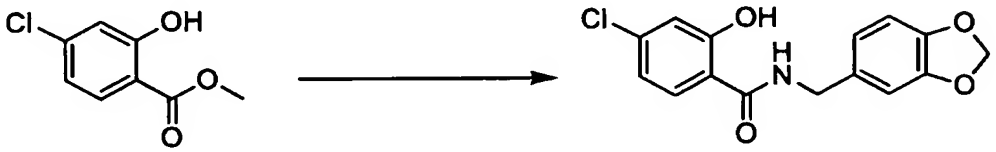
6.78 (d, J=8.5Hz, 1H), 6.95-7.00 (m, 2H), 10.95 (s, 1H)

MS(EI)E/Z329(M^+)

Preparation Example 8

Synthesis of 4-chloro-2-hydroxy-N-[3,4-(methylenedioxy)benzyl]benzamide

The title compound (BAK-G256) was obtained at a yield of 49% in the same manner as in Preparation Example 1.



BAK-G256

^{1}H-NMR($CDCl_3$)δ:

4.52 (d, J=5.6Hz, 2H), 5.96 (s, 2H), 6.42 (brs, 1H), 6.75-6.85 (m, 4H),

7.01 (d, J=2.1Hz, 1H), 7.24 (d, J=7.4Hz, 1H), 12.48 (s, 1H)

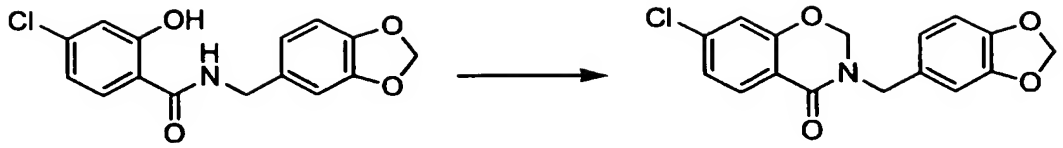
MS(EI)E/Z305(M^+)

Preparation Example 9

Synthesis of

7-chloro-2,3-dihydro-3-[3,4-(methylenedioxy)benzyl]-4H-1,3-benzoxazin-4-one

The title compound (BAK-G257) was obtained at a yield of 91% in the same manner as in Preparation Example 2.



BAK-G256 BAK-G257

^{1}H-NMR($CDCl_3$)δ:

4.65 (s, 2H), 5.11 (s, 2H), 5.95 (s, 2H), 6.75-6.85 (m, 3H),

6.98 (d, J=1.9Hz, 1H), 7.11 (dd, J=1.9, 8.4Hz, 1H), 7.94 (d, J=8.4Hz, 1H)

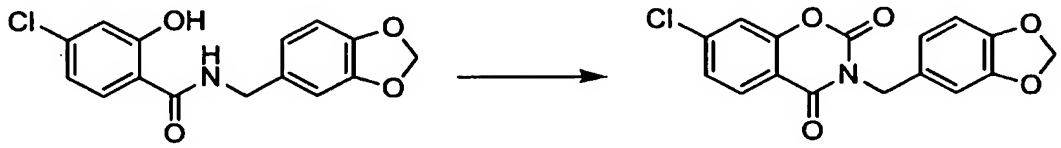
MS(EI)E/Z317(M^+)

Preparation Example 10

Synthesis of

7-chloro-3-[3,4-(methylenedioxy)benzyl]-2H-1,3-benzoxazin-2,4(3H)-dione

The title compound (BAK-G260) was obtained at a yield of 93% in the same manner as in Preparation Example 3.



BAK-G256 BAK-G260

^{1}H-NMR($CDCl_3$)δ:

5.09 (s, 2H), 5.93 (s, 2H), 6.75 (d, J=8.4Hz, 1H), 7.00-7.05 (m, 2H),

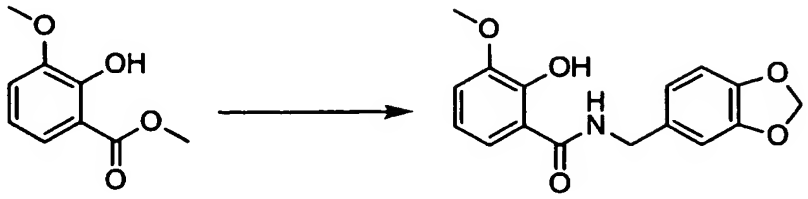
7.29 (d, J=1.9Hz, 1H), 7.34 (dd, J=1.9, 8.3Hz, 1H), 8.02 (d, J=8.3Hz, 1H)

MS(EI)E/Z331(M^+)

Preparation Example 11

Synthesis of 2-hydroxy-3-methoxy-N-[3,4-(methylenedioxy)benzyl]benzamide

The title compound (BAK-G261) was obtained at a yield of 52% in the same manner as in Preparation Example 1.



BAK-G261

^{1}H-NMR($CDCl_3$)δ:

3.90 (s, 3H), 4.54 (d, J=5.6Hz, 2H), 5.95 (s, 2H), 6.70-6.85 (m, 5H), 6.98 (dd, J=1.4, 8.0Hz, 1H), 7.07 (dd, J=1.4, 8.1Hz, 1H), 11.70 (s, 1H)

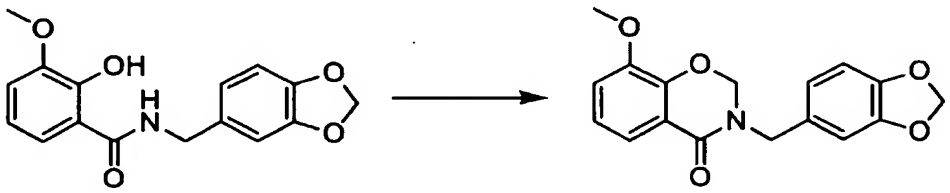
MS(EI)E/Z301(M^+)

Preparation Example 12

Synthesis of

2,3-dihydro-8-methoxy-3-[3,4-(methylenedioxy)benzyl]-4H-1,3-benzoxazin-4-one

The title compound (BAK-G263) was obtained at a yield of 97% in the same manner as in Preparation Example 2.



BAK-G261 BAK-G263

^{1}H-NMR($CDCl_3$)δ:

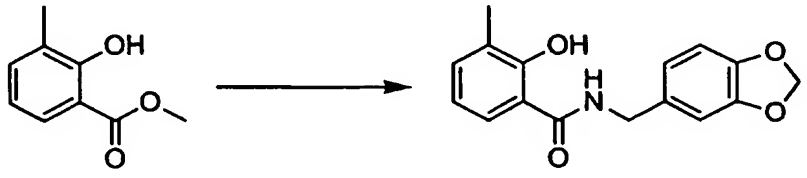
3.89 (s, 3H), 4.67 (s, 2H), 5.16 (s, 2H), 5.94 (s, 2H), 6.70-6.85 (m, 3H), 7.00-7.15 (m, 2H), 7.61 (dd, J=2.7, 6.6Hz, 1H)

MS(EI)E/Z313(M^+)

Preparation Example 13

Synthesis of 2-hydroxy-3-methyl-N-[3,4-(methylenedioxy)benzyl]benzamide

The title compound (BAK-G265) was obtained at a yield of 46% in the same manner as in Preparation Example 1.



BAK-G265

^{1}H-NMR($CDCl_3$)δ:

2.27 (s, 3H), 4.53 (d, J=5.6Hz, 2H), 5.96 (s, 2H), 6.48 (brs, 1H), 6.65-6.85 (m, 4H), 7.10-7.30 (m, 2H), 12.51 (s, 1H)

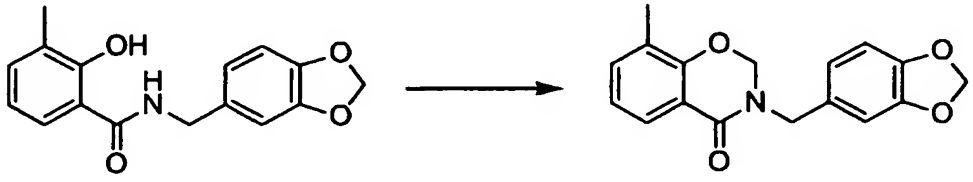
MS(EI)E/Z285(M^+)

Preparation Example 14

Synthesis of

2,3-dihydro-8-methyl-3-[3,4-(methylenedioxy)benzyl]-4H-1,3-benzoxazin-4-one

The title compound (BAK-G267) was obtained at a yield of 82% in the same manner as in Preparation Example 2.



BAK-G265 BAK-G267

^{1}H-NMR($CDCl_3$)δ:

2.21 (s, 3H), 4.66 (s, 2H), 5.12 (s, 2H), 5.95 (s, 2H), 6.70-6.85 (m, 3H),

7.02 (t, J=7.7Hz, 1H), 7.29 (dd, J=1.4, 7.7Hz, 1H), 7.85 (dd, J=1.4, 7.7Hz, 1H)

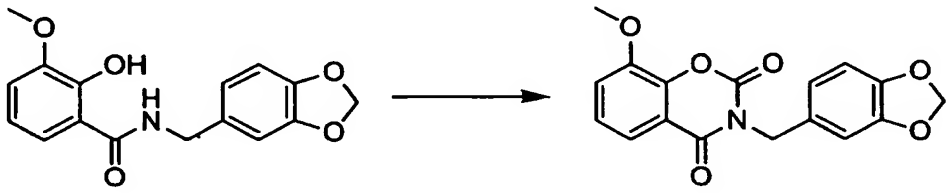
MS(EI)E/Z297(M^+)

Preparation Example 15

Synthesis of

8-methoxy-3-[3,4-(methylenedioxy)benzyl]-2H-1,3-benzoxazin-2,4(3H)-dione

The title compound (BAK-G268) was obtained at a yield of 94% in the same manner as in Preparation Example 3.



BAK-G261 BAK-G268

^{1}H-NMR($CDCl_3$)δ:

3.95 (s, 3H), 5.11 (s, 2H), 5.92(s, 2H), 6.74 (d, J=8.4Hz, 1H),

7.00-7.05 (m, 2H), 7.15-7.35 (m, 2H), 7.63 (dd, J=1.9, 7.5Hz, 1H)

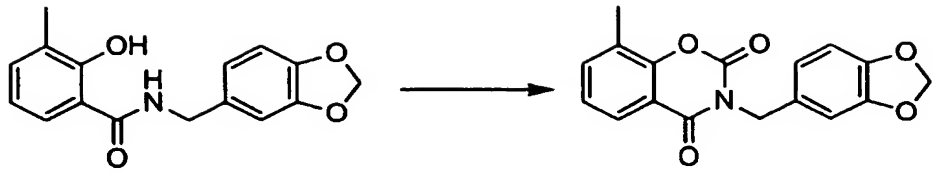
MS(EI)E/Z327(M^+)

Preparation Example 16

Synthesis of

8-methyl-3-[3,4-(methylenedioxy)benzyl]-2H-1,3-benzoxazin-2,4(3H)-dione

The title compound (BAK-G269) was obtained at a yield of 93% in the same manner as in Preparation Example 3.



BAK-G265 BAK-G269

^{1}H-NMR($CDCl_3$)δ:

2.41 (s ,3H), 5.12 (s, 2H), 5.92 (s, 2H), 6.75 (d, J=8.4Hz, 1H),

7.00-7.10 (m, 2H), 7.24 (t, J=7.3Hz, 1H), 7.52 (dd, J=1.4, 7.3Hz, 1H),

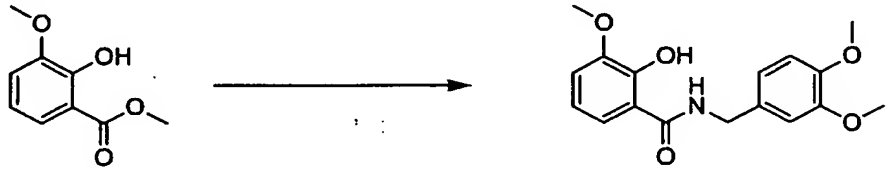
7.92 (dd ,J=1.4, 7.3Hz, 1H)

MS(EI)E/Z311(M^+)

Preparation Example 17

Synthesis of N-(3,4-dimethoxybenzyl)-2-hydroxy-3-methoxybenzamide

The title compound (BAK-G320) was obtained at a yield of 51% in the same manner as in Preparation Example 1.



BAK-G320

^{1}H-NMR($CDCl_3$)δ:

3.87 (s, 6H), 3.90 (s, 3H), 4.57 (d, J=5.6Hz, 2H), 6.75-6.95 (m, 5H),

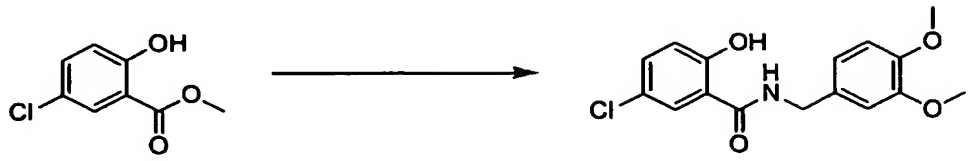
6.98 (dd, J=1, 4, 8.1Hz, 1H), 7.07 (dd, J=1.4, 8.1Hz, 1H), 11.81 (s, 1H)

MS(EI)E/Z317(M^+)

Preparation Example 18

Synthesis of 5-chloro-N-(3,4-dimethoxybenzyl)-2-hydroxybenzamide

The title compound (BAK-G332) was obtained at a yield of 79% in the same manner as in Preparation Example 1.



BAK-G332

^{1}H-NMR($CDCl_3$)δ:

3.89 (s, 6H), 4.56 (d, J=5.5Hz, 2H), 6.44 (brs, 1H), 6.80-6.90 (m, 3H), 6.95 (d, J=8.8Hz, 1H), 7.31 (d, J=2.5Hz, 1H), 7.34 (dd, J=2.5, 8.8Hz, 1H), 12.24 (s, 1H)

MS(EI)E/Z321(M^+)

Preparation Example 19

Synthesis of 5-chloro-2-hydroxy-N-[3,4-(methylenedioxy)benzyl]benzamide

The title compound (BAK-G293) was obtained at a yield of 26% in the same manner as in Preparation Example 1.

BAK-G293

^{1}H-NMR($CDCl_3$)δ:

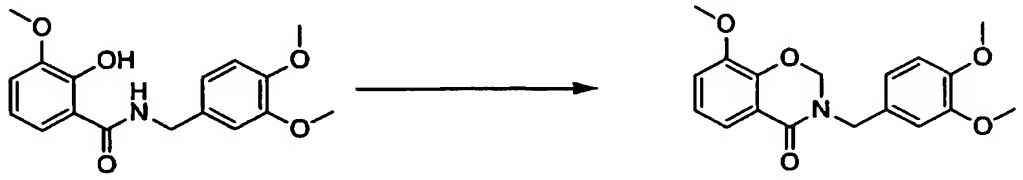
4.53 (d, J=5.6Hz, 2H), 5.98 (s, 2H), 6.43 (brs, 1H), 6.80-6.85 (m, 3H), 6.95(d, J=8.7Hz, 1H), 7.25-7.40 (m, 2H), 12.22 (s, 1H)

MS(EI)E/Z305(M^+)

Preparation Example 20

Synthesis of 3-(3,4-dimethoxybenzyl)-2,3-dihydro-8-methoxy-4H-1,3-benzoxazin-4-one

The title compound (BAK-G321) was obtained at a yield of 94% in the same manner as in Preparation Example 2.



BAK-G320 BAK-G321

^{1}H-NMR($CDCl_3$)δ:

3.86 (s, 3H), 3.87 (s, 3H), 3.89 (s, 3H), 4.70 (s, 2H), 5.17 (s, 2H),

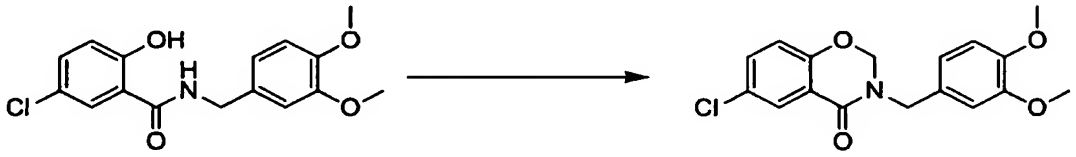
6.80-6.90 (m, 3H), 7.00-7.15 (m, 2H), 7.62 (dd, J=2.7, 6.7Hz, 1H)

MS(EI)E/Z329(M^+)

Preparation Example 21

Synthesis of 6-chloro-3-(3,4-dimethoxybenzyl)-2,3-dihydro-4H-1,3-benzoxazin-4-one

The title compound (BAK-G333) was obtained at a yield of 72% in the same manner as in Preparation Example 2.



BAK-G332 BAK-G333

^{1}H-NMR($CDCl_3$)δ:

3.86 (s, 3H), 3.87 (s, 3H), 4.69 (s, 2H), 5.10 (s, 2H), 6.80-6.90 (m, 3H),

6.91 (d, J=8.7Hz, 1H), 7.39 (dd, J=2.6, 8.7Hz, 1H), 7.99 (d, J=2.6Hz, 1H)

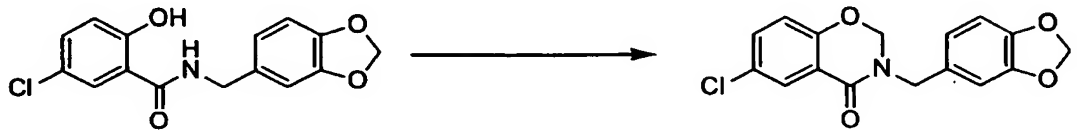
MS(EI)E/Z333(M^+)

Preparation Example 22

Synthesis of

6-chloro-2,3-dihydro-3-[3,4-(methylenedioxy)benzyl]-4H-1,3-benzoxazin-4-one

The title compound (BAK-G330) was obtained at a yield of 94% in the same manner as in Preparation Example 2.



BAK-G293 BAK-G330

^{1}H-NMR($CDCl_3$)δ:

4.65 (s, 2H), 5.10 (s, 2H), 5.95 (s, 2H), 6.75-6.85 (m, 3H),

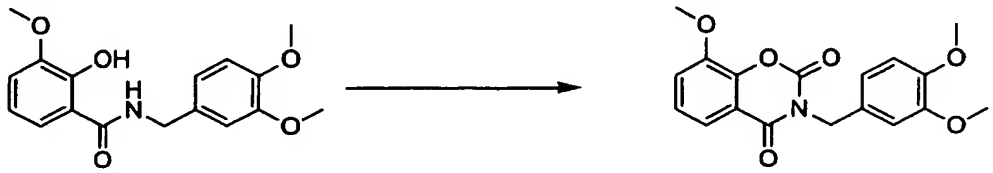
6.90 (d, J=8.7Hz, 1H), 7.39 (dd, J=2.6, 8.7Hz, 1H), 7.98 (d, J=2.6Hz, 1H)

MS(EI)E/Z317(M^+)

Preparation Example 23

Synthesis of 3-(3,4-dimethoxybenzyl)-8-methoxy-2H-1,3-benzoxazin-2,4(3H)-dione

The title compound (BAK-G322) was obtained at a yield of 95% in the same manner as in Preparation Example 3.



BAK-G320 BAK-G322

^{1}H-NMR($CDCl_3$)δ:

3.85 (s, 3H), 3.88 (s, 3H), 3.95 (s, 3H), 5.15 (s, 2H), 6.80 (d, J=8.7Hz, 1H),

7.10-7.35 (m, 4H), 7.64 (dd, J=1.9, 7.5Hz, 1H)

MS(EI)E/Z343(M^+)

Preparation Example 24

Synthesis of 6-chloro-3-(3,4-dimethoxybenzyl)-2H-1,3-benzoxazin-2,4(3H)-dione

The title compound (BAK-G340) was obtained at a yield of 75% in the same manner as in Preparation Example 3.

BAK-G332 BAK-G340

^{1}H-NMR($CDCl_3$)δ:

3.86 (s, 3H), 3.88 (s, 3H), 5.13 (s, 2H), 6.81 (d, J=8.8Hz, 1H),

7.10-7.20 (m, 2H), 7.23 (d, J=8.8Hz, 1H), 7.63 (dd, J=2.5, 8.8Hz, 1H),

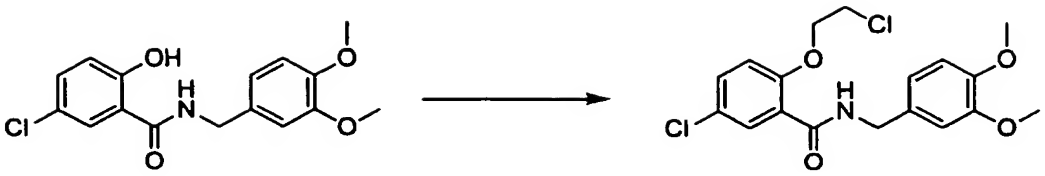
8.06 (d, J=2.5Hz, 1H)

MS(EI)E/Z347(M^+)

Preparation Example 25

Synthesis of 5-chloro-2-(2-chloroethoxy)-N-(3,4-dimethoxybenzyl)benzamide

A mixture of 1.15 g (3.57 mmol) of BAK-G332 obtained in Preparation Example 18, 0.59 ml (7.15 mmol) of 1-bromo-2-chloroetane, 1.48 g (10.71 mmol) of potassium carbonate, and 20 ml of DMF was stirred for 20 hours at 40 °C. Water was added to the reaction solution, the mixture was extracted with ethyl acetate, and the resulting organic layer was dried over anhydrous sodium sulfate. After concentration, the resulting crude product was purified by silica gel column chromatography (hexane : ethyl acetate = 1 : 1) to obtain 1.18 g (yield: 86%) of the title compound (BAK-G334).



BAK-G332 BAK-G334

^{1}H-NMR($CDCl_3$)δ:

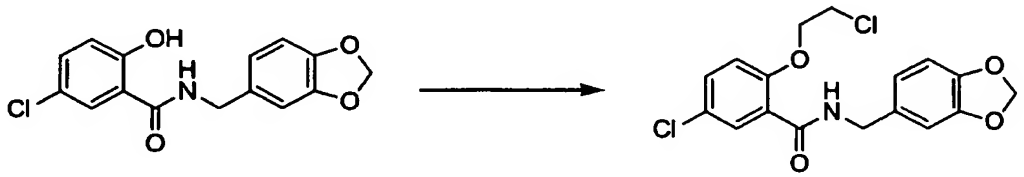
3.77 (t, J=4.8Hz, 2H), 3.87 (s, 3H), 3.88 (s, 3H), 4.30 (t, J=4.8Hz, 2H), 4.58 (d, J=5.6Hz, 2H), 6.80-6.95 (m, 4H), 7.37 (dd, J=2.8, 8.8Hz, 1H), 8.18 (brs, 1H), 8.22 (d, J=2.8Hz, 1H)

MS(EI)E/Z383(M^+)

Preparation Example 26

Synthesis of 5-chloro-2-(2-chloroethoxy)-N-[3,4-(methylendioxy)benzyl]benzamide

The title compound (BAK-G294) was obtained at a yield of 82% in the same manner as in Preparation Example 25.



BAK-G293 BAK-G294

^{1}H-NMR($CDCl_3$)δ:

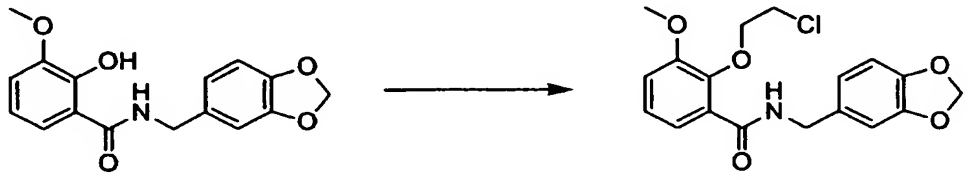
3.80 (t, J=4.8Hz, 2H), 4.31 (t, J=4.8Hz, 2H), 4.55 (d, J=5.6Hz, 2H), 5.94 (s, 2H), 6.70-6.90 (m, 4H), 7.37 (dd, J=2.8, 8.8Hz, H), 8.20 (brs, 1H), 8.21 (d, J=2.8Hz, 1H)

MS(EI)E/Z367(M^+)

Preparation Example 27

Synthesis of 2-(2-chloroethoxy)-3-methoxy-N-[3,4-(methylenedioxy)benzyl]benzamide

The title compound (BAK-G288) was obtained at a yield of 100% in the same manner as in Preparation Example 25.



BAK-G261 **BAK-G288**

^{1}H-NMR($CDCl_3$)δ:

3.71 (t, J=5.1Hz, 2H), 4.27 (t, J=5.1Hz, 2H), 4.56 (d, J=5.8Hz, 2H),
5.93 (s, 2H), 6.75(d, J=7.8Hz, 1H), 6.83 (dd, J=1.6, 7.8Hz, 1H),
6.87 (d, J=1.6Hz, 1H), 7.04 (dd, J=1.7, 7.9Hz, 1H), 7.18 (t, J=7.9Hz, 1H),
7.74 (dd, J=1.7, 7.9Hz, 1H), 8.28 (brs, 1H)

MS(EI)E/Z363(M^+)

Preparation Example 28

Synthesis of 2-(2-chloroethoxy)-4-methoxy-N-[3,4-(methylenedioxy)benzyl]benzamide

The title compound (BAK-G278) was obtained at a yield of 72% in the same manner as in Preparation Example 25.

BAK-G202 **BAK-G278**

^{1}H-NMR($CDCl_3$)δ:

3.79 (t, J=4.9Hz, 2H), 3.84 (s, 3H), 4.30 (t, J=4.9Hz, 2H),
4.55 (d, J=5.6Hz, 2H), 5.93 (s, 2H), 6.40 (d, J=2.3Hz, 1H),

6.64 (dd, J=2.3, 8.8Hz, 1H), 6.76 (d, J=7.8Hz, 1H),

6.85 (dd, J=1.6, 7.8Hz,1H), 6.88 (d, J=1.6Hz, 1H), 8.13 (brs, 1H),

8.21 (d, J=8.8Hz, 1H)

Preparation Example 29

Synthesis of 7-chloro-4-(3,4-dimethoxybenzyl)-3,4-dihydro-1,4-benzoxazepin-5(2H)-one

200 mg (5.00 mmol) of sodium hydride (60% oil) was added to 961 mg (2.50 mmol) of BAK-G334 obtained in Preparation Example 25 in 30 ml of toluene and the mixture was stirred for 20 hours at 100°C. Water was added to the reaction solution, the mixture was extracted with ethyl acetate, and the resulting organic layer was dried over anhydrous sodium sulfate. After concentration, the resulting crude product was purified by silica gel column chromatography (hexane : ethyl acetate = 3 : 2) to obtain 783 mg (yield: 90%) of the title compound (BAK-G335).

BAK-G334 **BAK-G335**

^{1}H-NMR($CDCl_3$)δ:

3.45 (t, J=5.3Hz, 2H), 3.88 (s, 3H), 3.89 (s, 3H), 4.13 (t, J=5.3Hz, 2H),

4.76 (s, 2H), 6.80-6.95 (m, 4H), 7.36 (dd, J=2.7, 8.6Hz, 1H),

7.85 (d, J=2.7Hz, 1H)

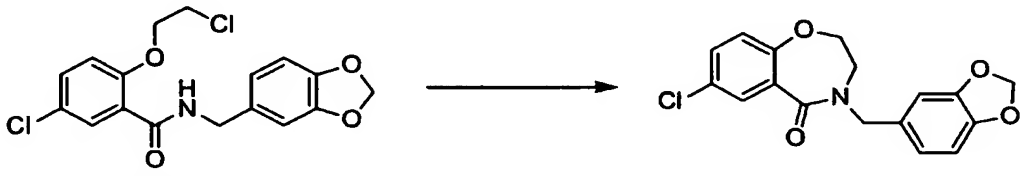
MS(EI)E/Z347(M^+)

Preparation Example 30

Synthesis of

7-chloro-3,4-dihydro-4-[3,4-(methylenedioxy)benzyl]-1,4-benzoxazepin-5(2H)-one

The title compound (BAK-G295) was obtained at a yield of 75% in the same manner as in Preparation Example 29.



BAK-G294 **BAK-G295**

^{1}H-NMR ($CDCl_3$)δ:

3.44 (t, J=4.9Hz, 2H), 4.18 (t, J=4.9Hz, 2H), 4.71 (s, 2H), 5.97 (s, 2H), 6.75-6.90 (m, 3H), 6.93 (d, J=8.6Hz, 1H), 7.36 (dd, J=2.7, 8.6Hz, 1H), 7.85 (d, J=2.7Hz, 1H)

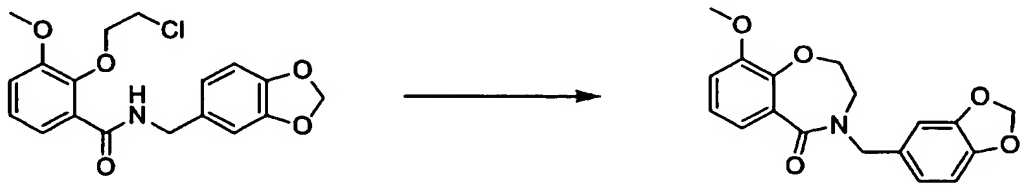
MS(EI) E/Z331 (M+)

Preparation Example 31

Synthesis of

3,4-dihydro-9-methoxy-4-[3,4-(methylenedioxy)benzyl]-1,4-benzoxazepin-5(2H)-one

The title compound (BAK-G290) was obtained at a yield of 75% in the same manner as in Preparation Example 29.



BAK-G288 **BAK-G290**

^{1}H-NMR($CDCl_3$)δ:

3.42 (t, J=5.3Hz, 2H), 3.87 (s, 3H), 4.20 (t, J=5.3Hz, 2H), 4.74 (s, 2H), 5.95 (s, 2H), 6.70-6.85 (m, 2H), 6.89 (d, J=1.2Hz, 1H),

7.03 (dd, J=1.7, 7.7Hz, 1H), 7.14 (t, J=7.7Hz, 1H), 7.39 (dd, J=1.7, 7.7Hz, 1H)

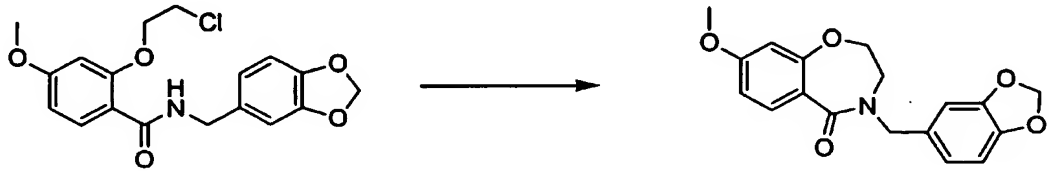
MS(EI)E/Z327(M^+)

Preparation Example 32

Synthesis of

3,4-dihydro-8-methoxy-4-[3,4-(methylenedioxy)benzyl]-1,4-benzoxazepin-5(4H)-one

The title compound (BAK-G282) was obtained at a yield of 87% in the same manner as in Preparation Example 29.



BAK-G278 **BAK-G282**

^{1}H-NMR($CDCl_3$)δ:

3.46 (t, J=4.7Hz, 2H), 3.82 (s, 3H), 4.20 (t, J=4.7Hz, 2H), 4.71 (s, 2H),

5.95 (s, 2H), 6.48 (d, J=2.5Hz, 1H), 6.71 (dd, J=2.5, 8.8Hz, 1H),

6.75-6.90 (m, 3H), 7.88 (d, J=8.8Hz, 1H)

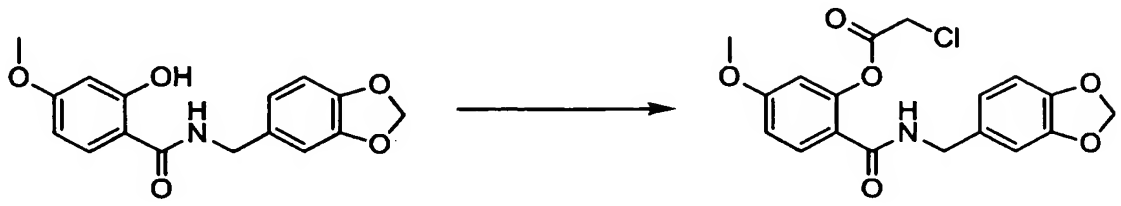
MS(EI)E/Z327(M^+)

Preparation Example 33

Synthesis of 3-methoxy-5-[[3,4-(methylenedioxy)benzyl]carbamoyl]phenyl chloroacetate

A mixture of 511.3 mg (1.70 mmol) of BAK-G202 obtained in Preparation Example 1, 0.59 ml (3.40 mmol) of DIEA, and 10 ml of dichloromethane was cooled with ice. 0.16 ml of chloroacetyl chloride was added dropwise to the mixture, followed by stirring for two hours while cooling with ice. Diluted hydrochloric acid was added to the reaction solution, the mixture was extracted with dichloromethane, and the resulting

organic layer was dried over anhydrous sodium sulfate. After concentration, the title compound (BAK-G272) was obtained as a crude product.



BAK-G202 BAK-G272

^{1}H-NMR($CDCl_3$)δ:

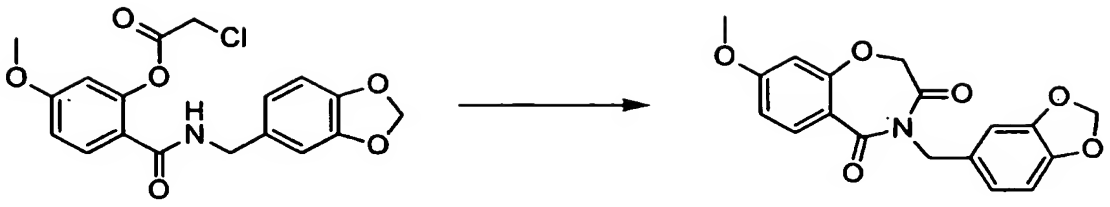
3.83 (s, 3H), 4.18 (s, 2H), 4.48 (d, J=5.7Hz, 2H), 5.95 (s, 2H), 6.45 (brs, 1H), 6.66 (d, J=2.5Hz, 1H), 6.75-6.85 (m, 3H), 6.85 (dd, J=2.5, 8.7Hz, 1H), 7.76 (d, J=8.7Hz, 1H)

Preparation Example 34

Synthesis of

8-methoxy-4-[(3,4-methylenedioxy)benzyl]-1,4-benzoxazepine-3,5(2H,4H)-dione

A mixture of BAK-G272 obtained as a crude product in Preparation Example 33, 469 mg (3.4 mmol) of potassium carbonate, and 50 ml of DMF was stirred for one hour at room temperature. 1 g of potassium carbonate was added to the reaction solution and the mixture was further stirred for one hour at room temperature. Water was added to the reaction solution, the mixture was extracted with ethyl acetate, and the resulting organic layer was dried over anhydrous sodium sulfate. After concentration, the resulting crude product was purified by silica gel column chromatography (hexane : ethyl acetate = 5 : 1) to obtain 327.3 mg (yield: 56%) of the title compound (BAK-G273).



BAK-G272 BAK-G273

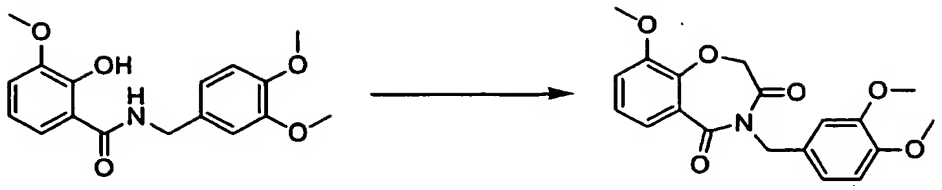
^{1}H-NMR($CDCl_3$)δ:

3.85 (s, 3H), 4.75 (s, 2H), 5.08 (s, 2H), 5.91 (s, 2H), 6.53 (d, J=2.5Hz, 1H), 6.70-6.80 (m, 2H), 6.85-6.95 (m, 2H), 8.14 (d, J=9.1Hz, 1H)

Preparation Example 35

Synthesis of 4-(3,4-dimethoxybenzyl)-9-methoxy-1,4-benzoxazepine-3,5(2H,4H)-dione

A mixture of 611.2 mg (1.93 mmol) of BAK-G320 obtained in Preparation Example 17, 0.67 ml (3.86 mmol) of DIEA, and 12 ml of dichloromethane was cooled with ice. 0.19 ml (2.33 mmol) of chloroacetyl chloride was added dropwise to the mixture, followed by stirring for two hours at room temperature. Diluted hydrochloric acid was added to the reaction solution, the mixture was extracted with dichloromethane, and the resulting organic layer was dried over anhydrous sodium sulfate. After concentration, the crude product was dissolved in DMF and 2 g of potassium carbonate was added to the the mixture, followed by stirring for two hours at 30 °C. Water was added to the reaction solution, the mixture was extracted with ethyl acetate, and the resulting organic layer was dried over anhydrous sodium sulfate. After concentration, the resulting crude product was purified by silica gel column chromatography (hexane : ethyl acetate = 3 : 2) to obtain 442.7 mg (yield: 64%) of the title compound (BAK-G323).



BAK-G320 BAK-G323

^{1}H-NMR($CDCl_3$)δ:

3.85 (s, 3H), 3.87 (s, 3H), 3.90 (s, 3H), 4.83 (s, 2H), 5.14 (s, 2H),

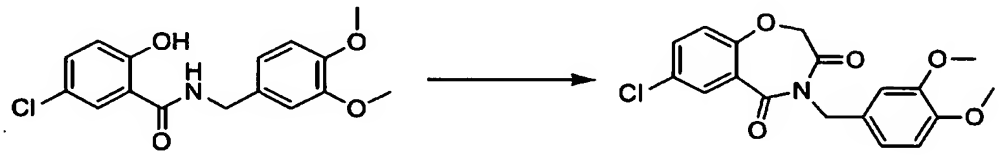
6.79 (d, J=8.8Hz, 1H), 7.00-7.20 (m, 4H), 7.64 (dd, J=2.0, 7.7Hz, 1H)

MS(EI)E/Z357(M^+)

Preparation Example 36

Synthesis of 7-chloro-4-(3,4-dimethoxybenzyl)-1,4-benzoxazepine-3,5(2H,4H)-dione

The title compound (BAK-G339) was obtained at a yield of 33% in the same manner as in Preparation Example 35.



BAK-G332 BAK-G339

^{1}H-NMR($CDCl_3$)δ:

3.85 (s, 3H), 3.87 (s, 3H), 4.77 (s, 2H), 5.13 (s, 2H), 6.79 (d, J=8.7Hz, 1H),

6.95-7.10 (m, 3H), 7.45 (dd, J=2.6, 8.7Hz, 1H), 8.13 (d, J=2.6Hz, 1H)

MS(EI)E/Z361(M^+)

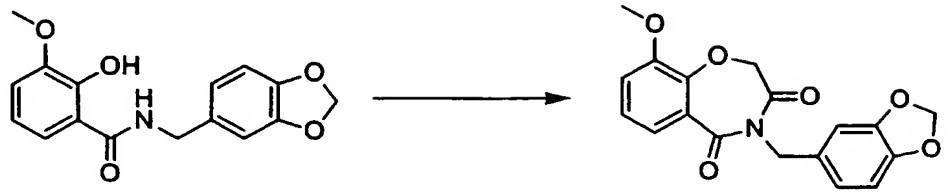
Preparation Example 37

Synthesis of

9-methoxy-4-[3,4-(methylenedioxy)benzyl]-1,4-benzoxazepine-3,5(2H,4H)-dione

The title compound (BAK-G287) was obtained at a yield of 72% in the same

manner as in Preparation Example 35.



BAK-G261 BAK-G287

^{1}H-NMR($CDCl_3$)δ:

3.90 (s, 3H), 4.82 (s, 2H), 5.11 (s, 2H), 5.91 (s, 2H), 6.73 (d, J=8.5Hz, 1H), 6.90-6.95 (m, 2H), 7.09 (dd, J=2.0, 7.6Hz, 1H), 7.16 (t, J=7.6, 1H), 7.64 (dd, J=2.0, 7.6Hz, 1H)

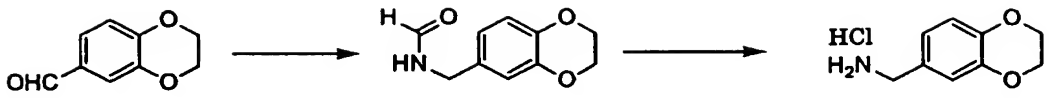
MS(EI)E/Z341(M^+)

Preparation Example 38

Synthesis of 1-(2,3-dihydro-1,4-benzodioxin-6-yl)methylamine hydrochloride

A mixture of 4.93 g (30.1 mmol) of 3,4-ethylenedioxybenzaldehyde, 15 ml of formamide, and 10 ml of formic acid was stirred for six hours at 130°C. Water was added to the reaction solution and the mixture was extracted with ethyl acetate. The resulting organic layer was washed with saturated aqueous solution of sodium hydrogencarbonate and dried over anhydrous sodium sulfate. After concentration, the resulting crude product was purified by silica gel column chromatography (hexane : ethyl acetate = 1 : 1) to obtain 2.36 g (yield: 41%) of 1-(2,3-dihydro-1,4-benzodioxin-6yl)methylamine (BAK-G366).

A mixture of 1.30 g (6.74 mmol) of the resulting BAK-G366, 10 ml of ethanol, and 1 ml of concentrated hydrochloric acid was refluxed for three hours. 20 ml of ether was added to the reaction solution at room temperature. The precipitated crystals were collected by filtration, washed with ether, and dried to obtain 1.06 g (yield: 78%) of the title compound (BAK-G369).



BAK-G366 BAK-G369

^{1}H-NMR(DMSO-d_6)δ:

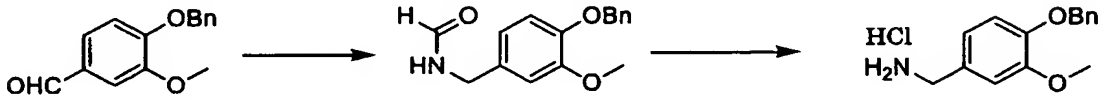
3.88 (s, 2H), 4.24 (s, 4H), 6.85-6.95 (m, 2H), 7.02 (d, J=1.6Hz, 1H),

8.21 (brs, 3H)

Preparation Example 39

Synthesis of 4-benzyloxy-3-methoxybenzylamine hydrochloride

The title compound (BAK-G388) was obtained at a yield of 38% in the same manner as in Preparation Example 38.



BAK-G387 BAK-G388

^{1}H-NMR(DMSO-d_6)δ:

3.79 (s, 3H), 3.92 (s, 2H), 5.10 (s, 2H), 6.95 (dd, J=1.8, 8.3Hz, 1H),

7.04 (d, J=8.3Hz, 1H), 7.23 (d, J=1.8Hz, 1H), 7.25-7.45 (m, 5H),

8.34 (brs, 3H)

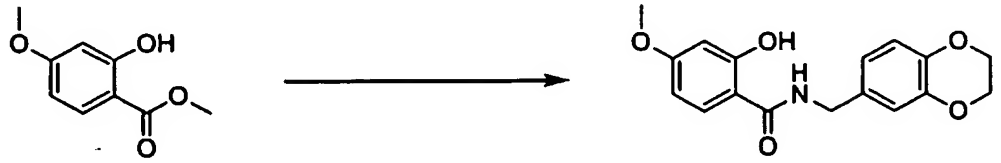
Preparation Example 40

Synthesis of

N-[(2,3-dihydro-1,4-benzodioxin-6-yl)methyl]-2-hydroxy-4-methoxybenzamide

A mixture of 307.7 mg (1.69 mmol) of methyl 4-methoxysalicylate, 341 mg (1.69 mmol) of BAK-G369 obtained in Preparation Example 38, 466 mg (3.38 mmol) of potassium carbonate, and 5 ml of DMSO was stirred for three hours at 140 °C. Water was added to the reaction solution, the mixture was extracted with ethyl acetate, and the

resulting organic layer was dried over anhydrous sodium sulfate. After concentration, the resulting crude product was purified by silica gel column chromatography (hexane : ethyl acetate = 3 : 1) to obtain 196 mg (yield: 37%) of the title compound (BAK-G371).



BAK-G371

^{1}H-NMR($CDCl_3$)δ:

3.81 (s, 3H), 4.25 (s, 4H), 4.50 (d, J=5.5Hz, 2H), 6.32 (brs, 1H),
6.38 (dd, J=2.5, 8.8Hz, 1H), 6.47 (d, J=2.5Hz, 1H), 6.70-6.90 (m, 3H),
7.23 (d, J=8.8Hz, 1H), 12.68 (s, 1H)

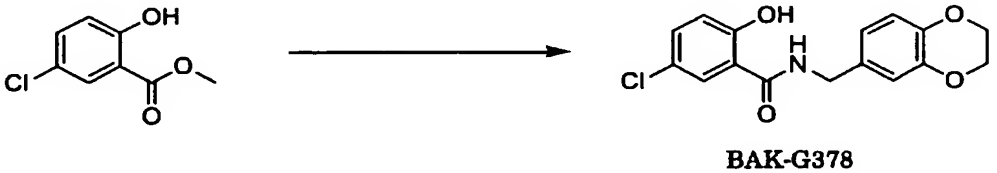
MS(EI) E/Z315 (M^+)

Preparation Example 41

Synthesis of

5-chloro-N-[(2,3-dihydro-1,4-benzodioxin-6-yl)methyl]-2-hydroxybenzamide

The title compound (BAK-G378) was obtained at a yield of 61% in the same manner as in Preparation Example 40.



BAK-G378

^{1}H-NMR($CDCl_3$)δ:

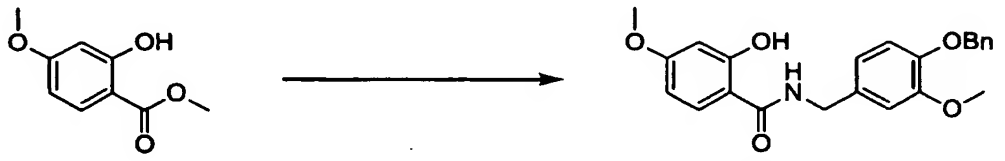
4.24 (s, 4H), 4.51 (d, J=5.8Hz, 2H), 6.75-6.90 (m, 3H), 6.94 (d, J=8.9Hz, 1H),
7.42 (dd, J=2.5, 8.9Hz, 1H), 7.88 (d, J=2.5Hz, 1H), 8.70 (brs, 1H),
12.80 (brs, 1H)

MS(EI)E/Z319(M^+)

Preparation Example 42

Synthesis of N-(4-benzyloxy-3-methoxybenzyl)-2-hydroxy-4-methoxybenzamide

The title compound (BAK-G391) was obtained at a yield of 31% in the same manner as in Preparation Example 40.



BAK-G391

^{1}H-NMR($CDCl_3$)δ:

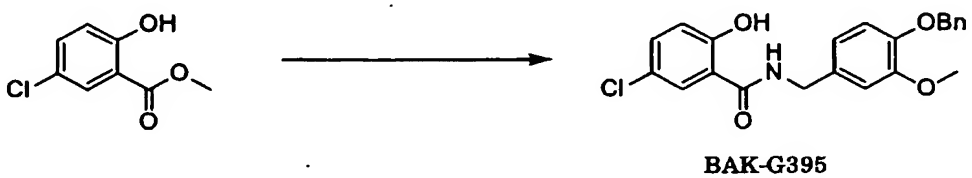
3.81 (s, 3H), 3.89 (s, 3H), 4.53 (d, J=5.5Hz, 2H), 5.16 (s, 2H), 6.29 (brs, 1H), 6.38 (dd, J=2.5, 8.9Hz, 1H), 6.47 (d, J=2.5Hz, 1H), 7.22 (d, J=8.9Hz, 1H), 7.25-7.50 (m, 5H), 12.68 (s, 1H)

MS(EI)E/Z393(M^+)

Preparation Example 43

Synthesis of N-(4-benzyloxy-3-methoxybenzyl)-5-chloro-2-hydroxybenzamide

The title compound (BAK-G395) was obtained at a yield of 54% in the same manner as in Preparation Example 40.



BAK-G395

^{1}H-NMR(DMSO-d_6)δ:

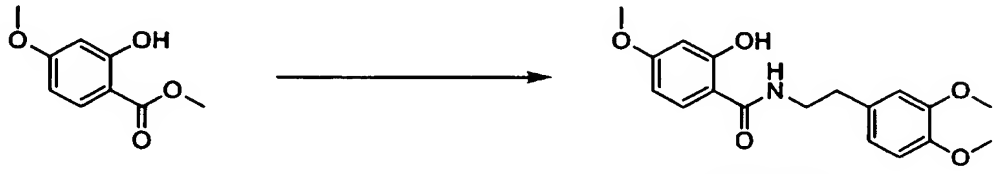
3.76 (s, 3H), 4.42 (m, 2H), 5.06 (s, 2H), 6.82 (dd, J=1.9, 8.2Hz, 1H), 6.90-7.00 (m, 3H), 7.30-7.50 (m, 6H), 7.96 (d, J=2.6Hz, 1H), 9.36 (brt, 1H), 12.56 (brs, 1H)

MS(EI)E/Z397(M^+)

Preparation Example 44

Synthesis of N-(3,4-dimethoxyphenethyl)-2-hydroxy-4-methoxybenzamide

The title compound (BAK-G386) was obtained at a yield of 24% in the same manner as in Preparation Example 1.



BAK-G386

^{1}H-NMR($CDCl_3$)δ:

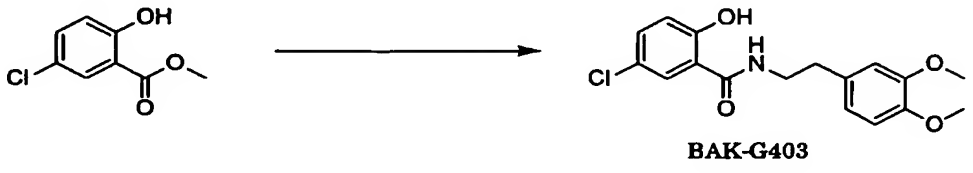
2.87 (t, J=6.8Hz, 2H), 3.67 (q, J=6.8Hz, 2H), 3.80 (s, 3H), 3.85 (s, 3H),
3.88 (s, 3H), 6.12 (brs, 1H), 6.36 (dd, J=2.5, 8.9Hz, 1H),
6.46 (d, J=2.5Hz, 1H), 6.70-6.90 (m, 3H), 7.08 (d, J=8.9Hz, 1H), 12.71 (s, 1H)

MS(EI)E/Z331(M^+)

Preparation Example 45

Synthesis of 5-chloro-N-(3,4-dimethoxyphenethyl)-2-hydroxybenzamide

The title compound (BAK-G403) was obtained at a yield of 47% in the same manner as in Preparation Example 1.



BAK-G403

^{1}H-NMR($CDCl_3$)δ:

2.88 (t, J=6.8Hz, 2H), 3.68 (q, J=6.8Hz, 2H), 3.87 (s, 3H), 3.88 (s, 3H),

6.28 (brs, 1H), 6.70-6.90 (m, 3H), 6.93 (d, J=8.9Hz, 1H),

7.17 (d, J=2.5Hz, 1H), 7.32 (dd, J=2.5, 8.9Hz1H), 12.24 (s, 1H)

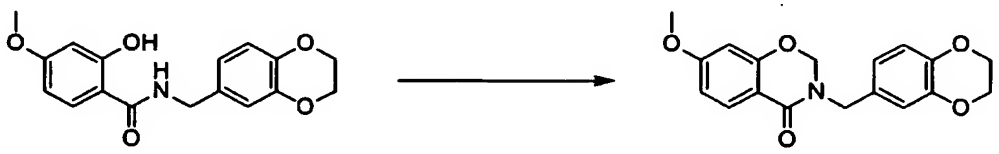
MS(EI)E/Z335(M^+)

Preparation Example 46

Synthesis of

3-[(2,3-dihydro-1,4-benzoxin-6-yl)methyl]-2,3-dihydro-7-methoxy-4H-1,3-benzoxazin-4-one

The title compound (BAK-G374) was obtained at a yield of 37% in the same manner as in Preparation Example 2.



BAK-G371 BAK-G374

^{1}H-NMR($CDCl_3$)δ:

3.83 (s, 3H), 4.24 (s, 4H), 4.63 (s, 2H), 5.09 (s, 2H), 6.42 (d, J=2.4Hz, 1H),

6.67 (dd, J=2.4, 8.7Hz, 1H), 6.80-6.90 (m, 3H), 7.92 (d, J=8.7Hz, 1H)

Preparation Example 47

Synthesis of

6-chloro-3-[(2,3-dihydro-1,4-benzodioxin-6-yl)methyl]-2,3-dihydro-4H-1,3-benzoxazin-4-one

The title compound (BAK-G379) was obtained at a yield of 76% in the same manner as in the Preparation Example 2.

BAK-G378 BAK-G379

^{1}H-NMR($CDCl_3$)δ:

4.25 (s, 4H), 4.64 (s, 2H), 5.10 (s, 2H), 6.75-6.90 (m, 3H),

6.90 (d, J=8.7Hz, 1H), 7.38 (dd, J=2.6, 8.7Hz, 1H), 7.97 (d, J=2.6Hz, 1H)

MS(EI)E/Z331(M^+)

Preparation Example 48

Synthesis of

3-[(2,3-dihydro-1,4-benzodioxin-6-yl)methyl]-7-methoxy-2H-1,3-benzoxazin-2,4(3H)-dion

The title compound (BAK-G377) was obtained at a yield of 61% in the same manner as in the Preparation Example 3.

BAK-G371 BAK-G377

^{1}H-NMR($CDCl_3$)δ:

3.89 (s, 3H), 4.22 (s, 4H), 5.07 (s, 2H), 6.68 (d, J=2.4Hz, 1H),

6.80 (d, J=8.2Hz, 1H), 6.88 (dd, J=2.4, 8.8Hz, 1H), 6.95-7.10 (m, 2H),

7.97 (d, J=8.8Hz, 1H)

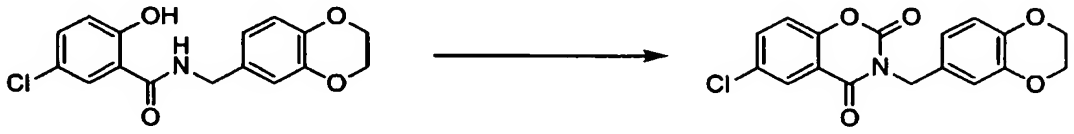
MS(EI)E/Z341(M^+)

Preparation Example 49

Synthesis of

6-chloro-3-[(2,3-dihydro-1,4-benzodioxin-6-yl)methyl]-2H-1,3-benzoxazin-2,4(3H)-dion

The title compound (BAK-G382) was obtained at a yield of 73% in the same manner as in the Preparation Example 3.



BAK-G378 BAK-G382

^{1}H-NMR($CDCl_3$)δ:

4.23 (s, 4H), 5.09 (s, 2H), 6.80 (d, J=8.2Hz, 1H), 6.95-7.05 (m, 2H), 7.22 (d, J=8.8Hz, 1H), 7.62 (dd, J=2.6, 8.8Hz, 1H), 8.05 (d, J=2.6Hz, 1H)

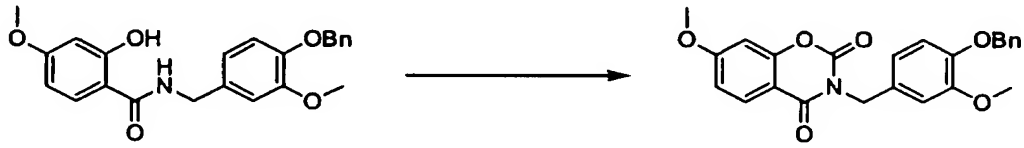
MS(EI)E/Z345(M^+)

Preparation Example 50

Synthesis of

3-(4-dibenzyloxy-3-methoxybenzyl)-7-methoxy-2H-1,3-benzoxazin-2,4(3H)-dione

The title compound (BAK-G393) was obtained at a yield of 94% in the same manner as in Preparation Example 3.



BAK-G391 BAK-G393

^{1}H-NMR($CDCl_3$)δ:

3.89 (s, 6H), 5.10 (s, 2H), 5.13 (s, 2H), 6.68 (d, J=2.3Hz, 1H),

6.81 (d, J=8.2Hz, 1H), 6.88 (dd, J=2.4, 8.8Hz, 1H),

7.04 (dd, J=2.0, 8.2Hz, 1H), 7.14 (d, J=2.0Hz, 1H), 7.25-7.45 (m, 5H),

7.97 (d, J=8.8Hz, 1H)

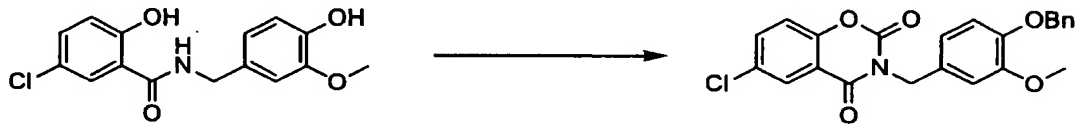
MS(EI)E/Z419(M^+)

Preparation Example 51

Synthesis of

3-(4-benzyloxy-3-methoxybenzyl)-6-chloro-2H-1,3-benzoxazin-2,4(3H)-dione

The title compound (BAK-G397) was obtained at a yield of 94% in the same manner as in Preparation Example 3.



BAK-G395 **BAK-G397**

^{1}H-NMR($CDCl_3$)δ:

3.89 (s, 3H), 5.11 (s, 2H), 5.13 (s, 2H), 6.81 (d, J=8.2Hz, 1H),

7.04 (dd, J=2.0, 8.2Hz, 1H), 7.13 (d, J=2.0Hz, 1H), 7.22 (d, J=8.8Hz, 1H),

7.25-7.45 (m, 5H), 7.63 (dd, J=2.5, 8.8Hz, 1H), 8.05 (d, J=2.5Hz, 1H)

MS(EI)E/Z423(M^+)

Preparation Example 52

Synthesis of 3-(3,4-dimethoxyphenethyl)-7-methoxy-2H-1,3-benzoxazin-2,4(3H)-dione

The title compound (BAK-G390) was obtained at a yield of 82% in the same manner as in Preparation Example 3.

BAK-G386 BAK-G390

^{1}H-NMR($CDCl_3$)δ:

2.95 (m, 2H), 3.86 (s, 3H), 3.87 (s, 3H), 3.91 (s, 3H), 4.21 (m, 2H),

6.71 (d, J=2.4Hz, 1H), 6.75-6.85 (m, 3H), 6.90 (dd, J=2.4, 8.8Hz, 1H),

7.97 (d, J=8.8Hz, 1H)

MS(EI) E/Z357 (M^+)

Preparation Example 53

Synthesis of 6-chloro-3-(3,4-dimethoxyphenethyl)-2H-1,3-benzoxazin-2,4(3H)-dione

The title compound (BAK-G405) was obtained at a yield of 81% in the same manner as in the Preparation Example 3.

BAK-G403 BAK-G405

^{1}H-NMR($CDCl_3$)δ:

2.95 (m, 2H), 3.86 (s, 3H), 3.88 (s, 3H), 4.23 (m, 2H), 6.75-6.90 (m, 3H),

7.24 (d, J=8.8Hz, 1H), 7.65 (dd, J=2.5, 8.8Hz, 1H), 8.04 (d, J=2.5Hz, 1H)

MS(EI)E/Z361(M^+)

Preparation Example 54

Synthesis of

3-(4-hydroxy-3-methoxybenzyl)-7-methoxy-2H-1,3-benzoxazin-2,4(3H)-dione

37 mg of 10% Pd-C was added to a mixture of 370 mg (0.883 mmol) of BAK-G393 obtained in Preparation Example 50, 14 ml of ethyl acetate, and 10ml of dichloromethane. The mixture was stirred under hydrogen atmosphere for three hours at room temperature. The reaction solution was filtrated through celite and the filtrate was concentrated. The resulting crude product was recrystallized from 24 ml of ethyl acetate-hexane (1:1) to obtain 188.5 mg (yield: 65%) of the title compound (BAK-G394).

BAK-G393 **BAK-G394**

^{1}H-NMR($CDCl_3$)δ:

3.88 (s, 3H), 3.89 (s, 3H), 5.10 (s, 2H), 5.60 (s, 1H), 6.68 (d, J=2.3Hz, 1H), 6.80-6.95 (m, 2H), 7.05-7.15 (m, 2H), 7.98 (d, J=8.8Hz, 1H)

MS(EI)E/Z329(M^+)

Preparation Example 55

Synthesis of

6-chloro-3-(4-hydroxy-3-methoxybenzyl)-2H-1,3-benzoxazin-2,4(3H)-dione

The title compound (BAK-G400) was obtained at a yield of 85% in the same manner as in Preparation Example 54.

BAK-G397 **BAK-G400**

^{1}H-NMR($CDCl_3$)δ:

3.89 (s, 3H), 5.11 (s, 2H), 5.62 (s, 1H), 6.85 (d, J=8.3Hz, 1H),

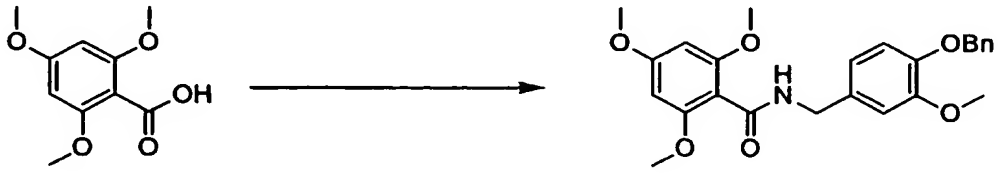
7.05-7.10 (m, 2H), 7.22 (d, J=8.8Hz, 1H), 7.63 (dd, J=2.5, 8.8Hz, 1H), 8.05 (d, J=2.5Hz, 1H)

MS(EI)E/Z333(M^+)

Preparation Example 56

Synthesis of N-(4-benzyloxy-3-methoxybenzyl)-2,4,6-trimethoxybenzamide

A mixture of 198.9 mg (0.938 mmol) of 2,4,6-trimethoxybenzoic acid, 263 mg (0.938 mmol) of BAK-G388 obtained in Preparation Example 39, 0.392 ml (2.25 mmol) of N,N-diisopropylethylamine, and 4 ml of DMF was cooled with ice. After addition of 0.17 ml (1.13 mmol) of diethylphosphate cyanide, the mixture was stirred for two hours while cooling with ice and for one hour at room temperature. Diluted hydrochloric acid was added to the reaction solution and the mixture was extracted with ethyl acetate. The resulting organic layer was washed with aqueous solution of sodium hydrogencarbonate and dried over anhydrous sodium sulfate. After concentration, the resulting crude product was purified by silica gel column chromatography (hexane : ethyl acetate = 2 : 1) to obtain 244.5 mg (yield: 60%) of the title compound (BAK-G401).



BAK-G337 **BAK-G401**

^{1}H-NMR($CDCl_3$)δ:

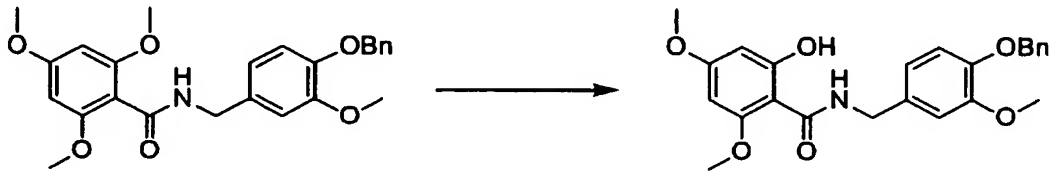
3.78 (s, 6H), 3.81 (s, 3H), 3.90 (s, 3H), 4.57 (d, J=5.8Hz, 2H), 5.15 (s, 2H), 5.98 (brt, 1H), 6.10 (s, 2H), 6.83 (m, 2H), 6.97 (s, 1H), 7.25-7.50 (m, 5H)

MS(EI)E/Z437(M^+)

Preparation Example 57

Synthesis of N-(4-benzyloxy-3-methoxybenzyl)-2-hydroxy-4,6-dimethoxybenzamide

878 mg (6.55 mmol) of lithium iodide was added to a mixture of 572 mg (1.31 mmol) of BAK-G401 obtained in Preparation Example 56 and 12 ml of 1,4-dioxane. The mixture was refluxed for 20 hours. Water was added to the reaction solution, the mixture was extracted with ethyl acetate, and the resulting organic layer was dried over anhydrous sodium sulfate. After concentration, the resulting crude product was purified by silica gel column chromatography (hexane : ethyl acetate = 1 : 1) to obtain 324 mg (yield: 58%) of the title compound (BAK-G402).



BAK-G401 **BAK-G402**

^{1}H-NMR($CDCl_3$)δ:

3.80 (s, 3H), 3.83 (s, 3H), 3.89 (s, 3H), 4.54 (d, J=5.6Hz, 2H), 5.15 (s, 2H), 5.95 (d, J=2.4Hz, 1H), 6.14 (d, J=2.4Hz, 1H), 6.80-6.95 (m, 3H), 7.25-7.50 (m, 5H), 8.36 (brt, 1H), 14.29 (s, 1H)

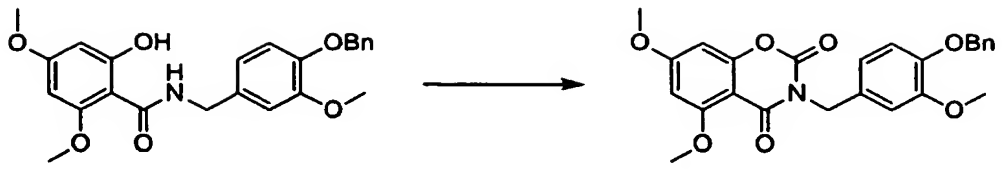
MS(EI)E/Z423(M^+)

Preparation Example 58

Synthesis of

3-(4-benzyloxy-3-methoxybenzyl)-5,7-dimethoxy-2H-1,3-benzoxazin-2,4(3H)-dione

The title compound (BAK-G404) was obtained at a yield of 92% in the same manner as in Preparation Example 3.



BAK-G402 BAK-G404

^{1}H-NMR($CDCl_3$)δ:

3.86 (s, 3H), 3.89 (s, 3H), 3.94 (s, 3H), 5.05 (s, 2H), 5.12 (s, 2H), 6.31 (s, 2H), 6.79 (d, J=8.2Hz, 1H), 7.06 (dd, J=2.0, 8.2Hz, 1H), 7.14 (d, J=2.0Hz, 1H), 7.25-7.45 (m, 5H)

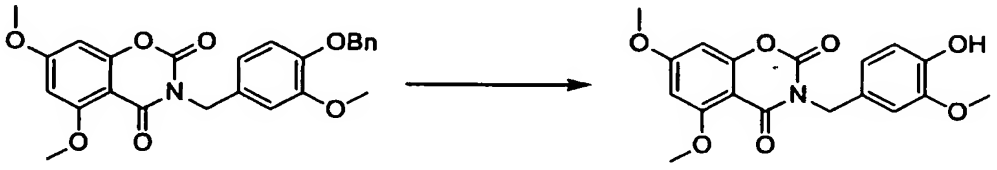
MS(EI)E/Z404(M^+)

Preparation Example 59

Synthesis of

3-(4-hydroxy-3-methoxybenzyl)-5,7-dimethoxy-2H-1,3-benzoxazin-2,4(3H)-dione

The title compound (BAK-G406) was obtained at a yield of 76% in the same manner as in the Preparation Example 54.



BAK-G404 BAK-G406

^{1}H-NMR($CDCl_3$)δ:

3.87 (s, 3H), 3.89 (s, 3H), 3.95 (s, 3H), 5.05 (s, 2H), 5.58 (s, 1H), 6.31 (s, 2H), 6.83 (d, J=8.6Hz, 1H), 7.05-7.15 (m, 2H)

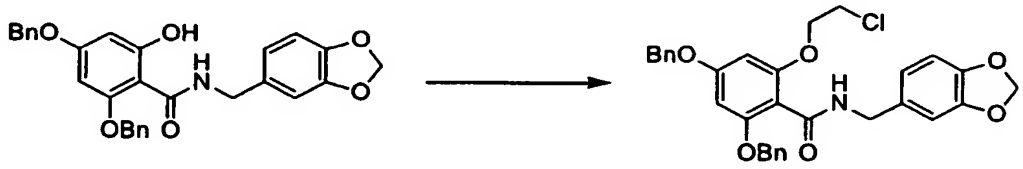
MS(EI)E/Z359(M^+)

Preparation Example 60

Synthesis of

2,4-bis(benzyloxy)-6-(2-chloroethoxy)-N-[3,4-(methylenedioxy)benzyl]benzamide

The title compound (BAK-G364) was obtained at a yield of 84% in the same manner as in Preparation Example 25.



BAK-G238 BAK-G364

^{1}H-NMR($CDCl_3$)δ:

3.74 (t, J=5.9Hz, 2H), 4.19 (t, J=5.9Hz, 2H), 5.92 (s, 2H),

6.04 (t, J=5.8Hz, 1H), 6.15 (d, J=2.0Hz, 1H), 6.25 (d, J=2.0Hz, 1H),

6.66 (d, J=7.9Hz, 1H), 6.77 (dd, J=1.5, 7.9Hz, 1H), 6.86 (d, J=1.5Hz, 1H),

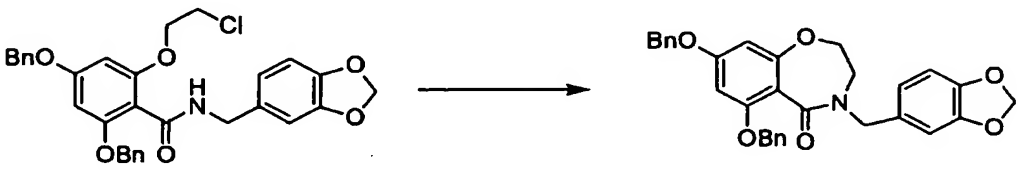
7.25-7.40 (m, 10H)

MS(EI)E/Z545(M^+)

Preparation Example 61

Synthesis of 6,8-bis(benzyloxy)-3,4-dihydro-4-[3,4-(methylenedioxy)benzyl]-1,4-benzoxazepin-5(2H)-one

The title compound (BAK-G367) was obtained at a yield of 76% in the same manner as in the Preparation Example 29.



BAK-G364 BAK-G367

^{1}H-NMR($CDCl_3$)δ:

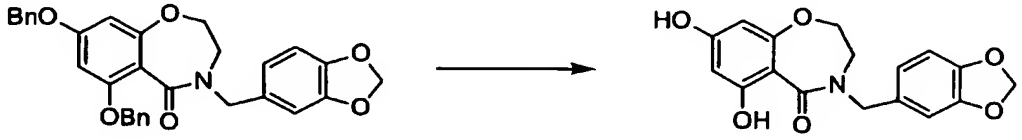
3.39 (t, J=5.6Hz, 2H), 3.98 (t, J=5.6Hz, 2H), 4.74 (s, 2H), 4.99 (s, 2H), 5.16 (s, 2H), 5.95 (s, 2H), 6.26 (d, J=2.3Hz, 1H), 6.44 (d, J=2.3Hz, 1H), 6.75 (d, J=7.9Hz, 1H), 6.83 (dd, J=1.5, 7.9Hz, 1H), 6.94 (d, J=1.5Hz, 1H), 7.25-7.50 (m, 10H)

MS(EI)E/Z509(M^+)

Preparation Example 62

Synthesis of 3,4-dihydro-6,8-dihydroxy-4-[3,4-(methylenedioxy)benzyl]-1,4-benzoxazepin-5(2H)-one

66 mg of 10% Pd-C was added to a mixture of 660 mg (1.30 mmol) of BAK-G367 obtained in Preparation Example 61 and 12 ml of ethyl acetate. The mixture was stirred under hydrogen atmosphere for 20 hours at room temperature. The reaction solution was filtrated through celite and the filtrate was concentrated. The resulting crude product was purified by silica gel column chromatography (hexane : ethyl acetate = 1 : 1) to obtain 357.3 mg (yield: 83%) of the title compound (BAK-G372).



BAK-G367 **BAK-G372**

^{1}H-NMR($CDCl_3$)δ:

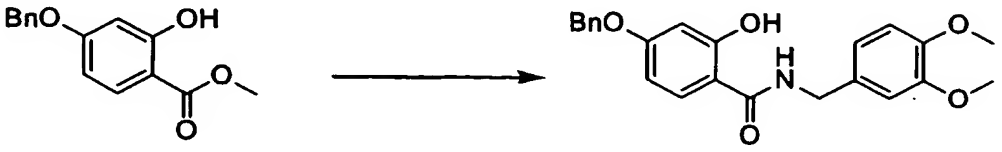
3.46 (t, J=4.9Hz, 2H), 4.20 (t, J=4.9Hz, 2H), 4.68 (s, 2H), 5.30 (s, 1H), 5.97 (s, 2H), 6.03 (d, J=2.5Hz, 1H), 6.20 (d, J=2.5Hz, 1H), 6.75-6.85 (m, 3H), 11.80 (s, 1H)

MS(EI)E/Z329(M^+)

Preparation Example 63

Synthesis of 4-benzyloxy-N-(3,4-dimethoxybenzyl)-2-hydroxybenzamide

The title compound (BAK-G441) was obtained at a yield of 18% in the same manner as in Preparation Example 1.



BAK-G365-1 **BAK-G441**

^{1}H-NMR($CDCl_3$)δ:

3.88 (s, 6H), 4.54 (d, J=5.5Hz, 2H), 5.06 (s, 2H), 6.33 (brt, 1H),

6.45 (dd, J=2.5, 8.5Hz, 1H), 6.56 (d, J=2.5Hz, 1H), 6.80-6.95 (m, 3H),

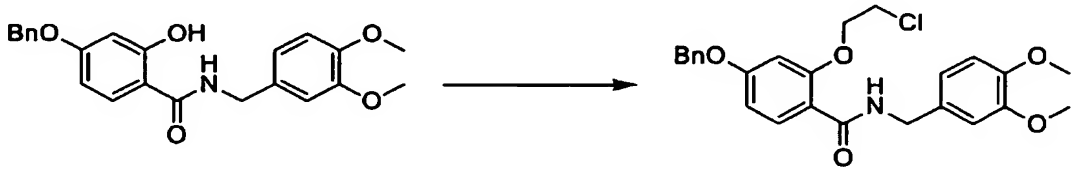
7.24 (d, J=8.8Hz, 1H), 7.30-7.45 (m, 5H), 12.67 (s, 1H)

MS(EI)E/Z393(M^+)

Preparation Example 64

Synthesis of 4-benzyloxy-2-(2-chloroethoxy)-N-(3,4-dimethoxybenzyl)benzamide

The title compound (BAK-G442) was obtained at a yield of 92% in the same manner as in Preparation Example 25.



BAK-G441 **BAK-G442**

^{1}H-NMR($CDCl_3$)δ:

3.74 (t, J=4.8Hz, 2H), 3.86 (s, 3H), 3.87 (s, 3H), 4.26 (t, J=4.8Hz, 2H),

4.58 (d, J=5.6Hz, 2H), 5.09 (s, 2H), 6.48 (d, J=2.3Hz, 1H),

6.71 (dd, J=2.3, 8.8Hz, 1H), 6.82 (d, J=8.7Hz, 1H), 6.90-7.00 (m, 2H),

7.30-7.45 (m, 5H), 8.14 (brt, 1H), 8.22 (d, J=8.8Hz, 1H)

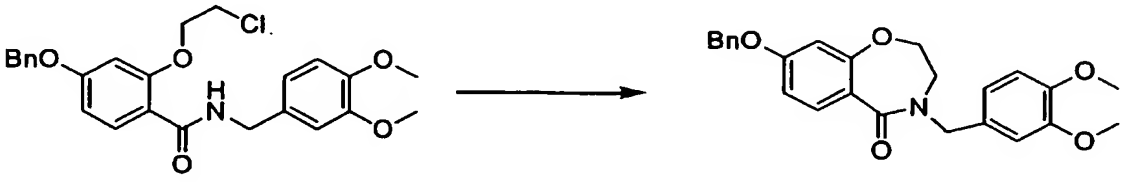
MS(EI)E/Z455(M^+)

Preparation Example 65

Synthesis of

8-benzyloxy-4-(3,4-dimethoxybenzyl)-3,4-dihydro-1,4-benzoxazepin-5(2H)-one

The title compound (BAK-G444) was obtained at a yield of 91% in the same manner as in Preparation Example 29.



BAK-G442 **BAK-G444**

^{1}H-NMR($CDCl_3$)δ:

3.46 (t, J=5.2Hz, 2H), 3.87 (s, 3H), 3.88 (s, 3H), 4.14 (t, J=5.2Hz, 2H),

4.75 (s, 2H), 5.07 (s, 2H), 6.75-6.95 (m, 4H), 7.30-7.45 (m, 5H),

7.87 (d, J=8.8Hz, 1H)

MS(EI)E/Z419(M^+)

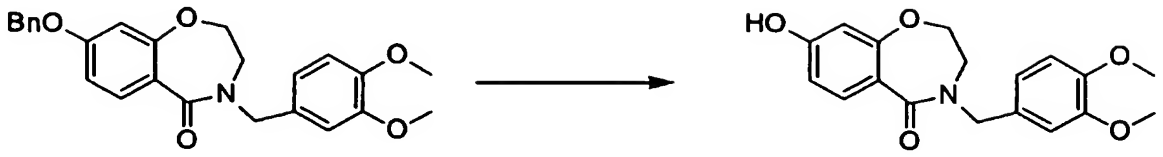
Preparation Example 66

Synthesis of

3,4-dihydro-4-(3,4-dimethoxybenzyl)-8-hydroxy-1,4-benzoxazepin-5(2H)-one

48 mg of 10% Pd-C was added to a mixture of 480 mg (1.15 mmol) of BAK-G444 obtained in Preparation Example 65 and 10 ml of ethyl acetate. The mixture was stirred under hydrogen atmosphere for 20 hours. The reaction solution was filtrated through celite and the filtrate was concentrated. The resulting crude product was purified by silica gel column chromatography (hexane : ethyl acetate = 1 : 2) to obtain 334.5 mg

(yield: 88%) of the title compound (BAK-G445).



BAK-G444 **BAK-G445**

^{1}H-NMR($CDCl_3$)δ:

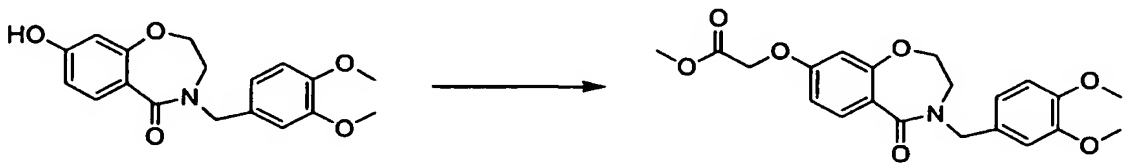
3.46 (t, J=5.2Hz, 2H), 3.86 (s, 3H), 3.88 (s, 3H), 4.13 (t, J=5.2Hz, 2H), 4.75 (s, 2H), 6.39 (s, 1H), 6.45 (d, J=2.5Hz, 1H), 6.62 (dd, J=2.5, 8.6Hz, 1H), 6.75-6.95 (m, 3H), 7.78 (d, J=8.6Hz, 1H)

MS(EI)E/Z329(M^+)

Preparation Example 67

Synthesis of methyl [[4-(3,4-dimethoxybenzyl)-2,3,4,5-tetrahydro-5-oxo-1,4-benzoxazepin-8-yl]oxy]acetate

A mixture of 259.3 mg (0.788 mmol) of BAK-G445 obtained in Preparation Example 66, 326 mg (2.36 mmol) of potassium carbonate, 0.15 ml (1.58 mmol) of methyl bromoacetate, and 4 ml of DMF was stirred for four hours at room temperature. Water was added to the reaction solution, the mixture was extracted with ethyl acetate, and the resulting organic layer was dried over anhydrous sodium sulfate. After concentration, the resulting crude product was purified by silica gel column chromatography (hexane : ethyl acetate = 1 : 1) to obtain 323.3 mg (yield: 100%) of the title compound (BAK-G460).



BAK-G445 **BAK-G460**

^{1}H-NMR($CDCl_3$)δ:

3.47 (t, J=5.1Hz, 2H), 3.81 (s, 3H), 3.87 (s, 3H), 3.88 (s, 3H),

4.14 (t, J=5.1Hz, 2H), 4.65 (s, 2H), 4.75 (s, 2H), 6.49 (d, J=2.5Hz, 1H),

6.72 (dd, J=2.5, 8.8Hz, 1H), 6.75-6.95 (m, 3H), 7.89 (d, J=8.8Hz, 1H)

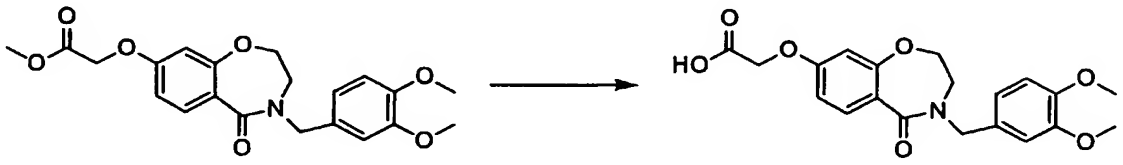
MS(EI)E/Z401(M^+)

Preparation Example 68

Synthesis of

[[4-(3,4-dimethoxybenzyl)-2,3,4,5-tetrahydro-5-oxo-1,4-benzoxazepin-8-yl]oxy]acetic acid

400 mg of sodium hydroxide and 3 ml of water were added to 315 mg (0.786 mmol) of BAK-G460 obtained in Preparation Example 67 in 7 ml of methanol and the mixture was refluxed for three hours. The reaction solution was acidified by addition of diluted hydrochloric acid, the mixture was extracted with ethyl acetate, and the resulting organic layer was dried over anhydrous sodium sulfate. After concentration, the resulting crude product was recrystallized from 10 ml of ethanol to obtain 227.2 mg (yield: 75%) of the title compound (BAK-G462).



BAK-G460 **BAK-G462**

^{1}H-NMR(DMSO-d_6)δ:

3.49 (t, J=4.6Hz, 2H), 3.72 (s, 3H), 3.73 (s, 3H), 4.19 (t, J=4.6Hz, 2H),

4.65 (s, 2H), 4.72 (s, 2H), 6.50 (d, J=2.5Hz, 1H), 6.73 (dd, J=2.5, 8.8Hz, 1H),

6.80-6.95 (m, 3H), 7.69 (d, J=8.8Hz, 1H)

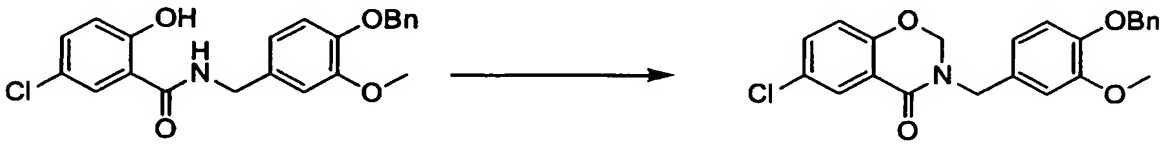
MS(EI)E/Z387(M^+)

Preparation Example 69

Synthesis of

3-[(4-benzyloxy-3-methoxy)benzyl]-6-chloro-2,3-dihydro-4H-1,3-benzoxazin-4-one

The title compound (BAK-G454) was obtained at a yield of 88% in the same manner as in Preparation Example 1.



BAK-G395 **BAK-G454**

^{1}H-NMR($CDCl^3$)δ:

3.87 (s, 3H), 4.68 (s, 2H), 5.09 (s, 2H), 5.15 (s, 2H), 6.75-6.95 (m, 4H), 7.30-7.50 (m, 6H), 7.98 (d, J=2.6Hz, 1H)

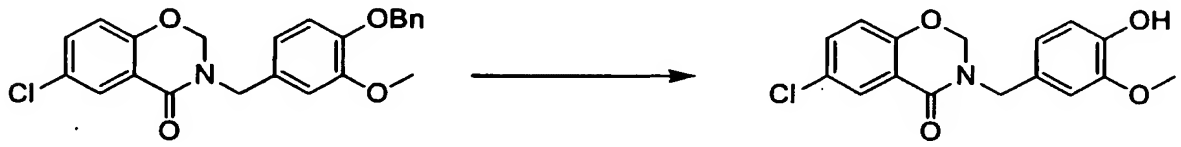
MS(EI)E/Z409(M^+)

Preparation Example 70

Synthesis of

6-chloro-2,3-dihydro-3-[(4-hydroxy-3-methoxy)benzyl]-4H-1,3-benzoxazin-4-one

The title compound (BAK-G456) was obtained at a yield of 71% in the same manner as in Preparation Example 66.



BAK-G454 **BAK-G456**

^{1}H-NMR($CDCl^3$)δ:

3.87 (s, 3H), 4.67 (s, 2H), 5.09 (s, 2H), 5.64 (s, 1H), 6.75-6.95 (m, 4H), 7.39 (dd, J=2.6, 8.7Hz, 1H), 7.98 (d, J=2.6Hz, 1H)

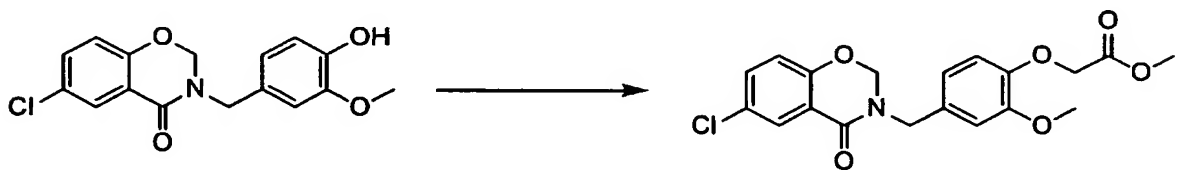
MS(EI)E/Z319(M^+)

Preparation Example 71

Synthesis of methyl

[4-[[6-chloro-4-oxo-2H-1,3-benzoxazin-3(4H)-yl]methyl]-2-methoxyphenoxy]acetate

The title compound (BAK-G459) was obtained at a yield of 100% in the same manner as in Preparation Example 67.



BAK-G456 **BAK-G459**

^{1}H-NMR($CDCl_3$)δ:

3.80 (s, 3H), 3.87 (s, 3H), 4.69 (s, 4H), 5.10 (s, 2H), 6.75-6.95 (m, 4H), 7.40 (dd, J=2.6, 8.7Hz, 1H), 7.98 (d, J=2.6Hz, 1H)

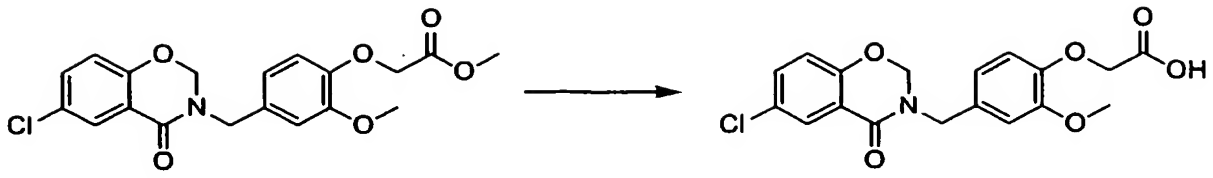
MS(EI)E/Z391(M^+)

Preparation Example 72

Synthesis of

[4-[[6-chloro-4-oxo-2H-1,3-benzoxazin-3(4H)-yl]methyl]-2-methoxyphenoxy]acetic acid

The title compound (BAK-G461) was obtained at a yield of 67% in the same manner as in Preparation Example 68.



BAK-G459 **BAK-G461**

^{1}H-NMR(DMSO-d_6)δ:

3.75 (s, 3H), 4.61 (s, 2H), 4.62 (s, 2H), 5.33 (s, 2H), 6.82 (m, 2H),

6.96 (s, 1H), 7.12 (d, J=8.7Hz, 1H), 7.59 (dd, J=2.6, 8.7Hz, 1H),

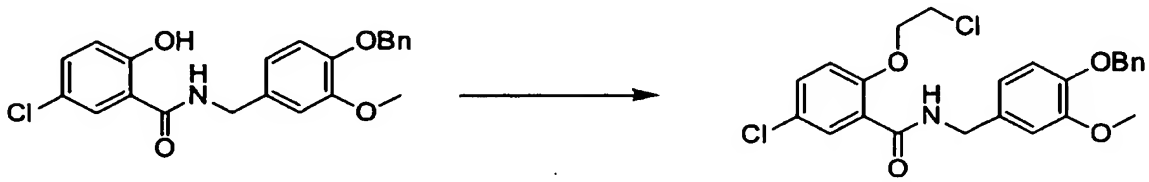
7.78 (d, J=2.6Hz, 1H)

MS(EI)E/Z377(M^+)

Preparation Example 73

Synthesis of N-[(4-benzyloxy-3-methoxy)benzyl]-5-chloro-2-(2-chloroethoxy) benzamide

The title compound (BAK-G471) was obtained at a yield of 88% in the same manner as in Preparation Example 25.



BAK-G395 **BAK-G471**

^{1}H-NMR($CDCl_3$)δ:

3.73 (t, J=4.8Hz, 2H), 3.88 (s, 3H), 4.29 (t, J=4.8Hz, 2H),

4.57 (d, J=5.6Hz, 2H), 5.15 (s, 2H), 6.75-6.95 (m, 4H), 7.25-7.50 (m, 6H),

8.18 (brt, 1H), 8.21 (d, J=2.8Hz, 1H)

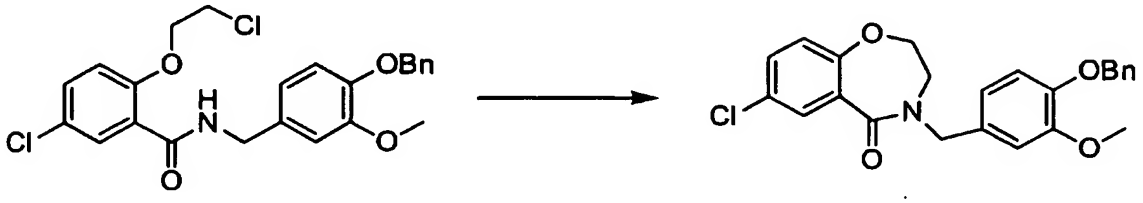
MS(EI)E/Z459(M^+)

Preparation Example 74

Synthesis of

4-[(4-benzyloxy-3-methoxy)benzyl]-7-chloro-3,4-dihydro-1,4-benzoxazepin-5(2H)-one

The title compound (BAK-G472) was obtained at a yield of 86% in the same manner as in Preparation Example 29.



BAK-G471 **BAK-G472**

^{1}H-NMR($CDCl_3$)δ:

3.44 (t, J=4.9Hz, 2H), 3.88 (s, 3H), 4.12 (t, J=4.9Hz, 2H), 4.74 (s, 2H), 5.15 (s, 2H), 6.75-7.00 (m, 4H), 7.25-7.50 (m, 6H), 7.84 (d, J=2.7Hz, 1H)

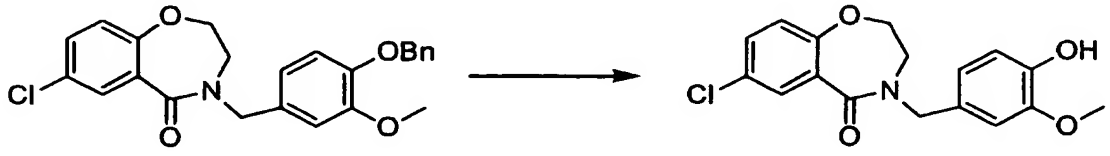
MS(EI)E/Z423(M^+)

Preparation Example 75

Synthesis of

7-chloro-3,4-dihydro-4-[(4-hydroxy-3-methoxy)benzyl]-1,4-benzoxazepin-5(2H)-one

The title compound (BAK-G473) was obtained at a yield of 89% in the same manner as in Preparation Example 66.



BAK-G472 **BAK-G473**

^{1}H-NMR($CDCl_3$)δ:

3.45 (t, J=4.9Hz, 2H), 3.88 (s, 3H), 4.12 (t, J=4.9Hz, 2H), 4.73 (s, 2H),

5.65 (s, 1H), 6.80 (dd, J=1.8, 8.0Hz, 1H), 6.85-7.00 (m, 3H),

7.36 (dd, J=2.7, 8.7Hz, 1H), 7.84 (d, J=2.7Hz, 1H)

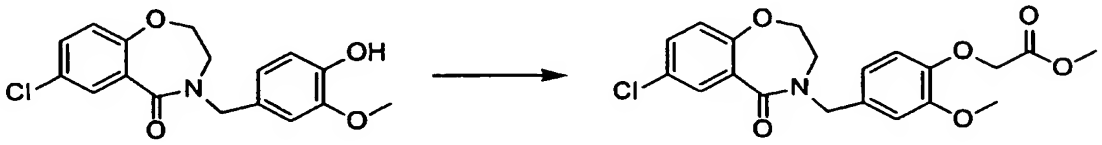
MS(EI)E/Z333(M^+)

Preparation Example 76

Synthesis of methyl

[4-[[7-chloro-2,3-dihydro-5-oxo-1,4-benzoxazepin-4(5H)-yl]methyl]-2-methoxyphenoxy]acetate

The title compound (BAK-G474) was obtained at a yield of 100% in the same manner as in Preparation Example 67.



BAK-G473 **BAK-G474**

^{1}H-NMR($CDCl_3$)δ:

3.45 (t, J=5.3Hz, 2H), 3.80 (s, 3H), 3.88 (s, 3H), 4.14 (t, J=5.3Hz, 2H),

4.70 (s, 2H), 4.75 (s, 2H), 6.77 (d, J=8.1Hz, 1H), 6.83 (dd, J=1.7, 8.1Hz, 1H),

6.94 (d, J=8.6Hz, 1H), 6.95 (d, J=1.7Hz, 1H), 7.37 (dd, J=2.7, 8.6Hz, 1H),

7.84 (d, J=2.7Hz, 1H)

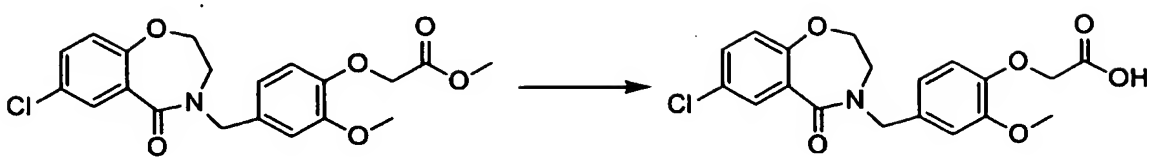
MS(EI)E/Z405(M^+)

Preparation Example 77

Synthesis of [4-[[7-chloro-2,3-dihydro-5-oxo-1,4-benzoxazepin-4(5H)-yl]methyl]-2-methoxyphenoxy]acetic acid

The title compound (BAK-G475) was obtained at a yield of 79% in the same

manner as in Preparation Example 68.



BAK-G474 BAK-G475

^{1}H-NMR(DMSO-d_6)δ:

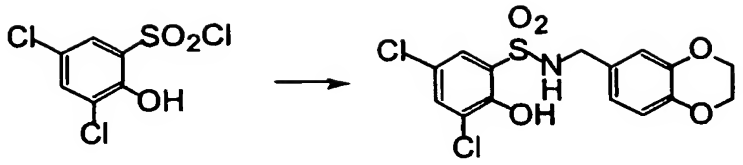
3.52 (t, J=4.8Hz, 2H), 3.76 (s, 3H), 4.22 (t, J=4.8Hz, 2H), 4.64 (s, 2H), 4.67 (s, 2H), 6.83 (brs, 1H), 6.97 (brs, 1H), 7.07 (d, J=8.7Hz, 1H), 7.53 (dd, J=2.7, 8.7Hz, 1H), 7.69 (d, J=2.7Hz, 1H)

MS(EI)E/Z391(M^+)

Preparation Example 78

Synthesis of 3,5-dichloro-N-[(2,3-dihydro-1,4-benzodioxin-6-yl)methyl]-2-hydroxy-benzenesulfonamide

A mixture of 1.00 g (3.82 mmol) of 3,5-dichloro-2-hydroxybenzenesulfonyl chloride, 771 mg (3.82 mmol) of BAK-G369 obtained in Preparation Example 38, 1.60 ml (11.5 mmol) of triethylamine, and 40.0 ml of chloroform was stirred for 16.5 hours at room temperature. 2 mol/l of hydrochloric acid was added to the reaction solution and the mixture was extracted with chloroform. The resulting organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate. After concentration, the resulting crude product was purified by silica gel column chromatography (hexane : ethyl acetate = 2 : 1) to obtain 1.45 g (yield: 97%) of the title compound (BAK-KA254).



BAK-KA254

^{1}H-NMR($CDCl_3$)δ:

4.09 (s, 2H), 4.22 (s, 4H), 6.58-6.76 (m, 3H), 7.50 (brs, 1H)

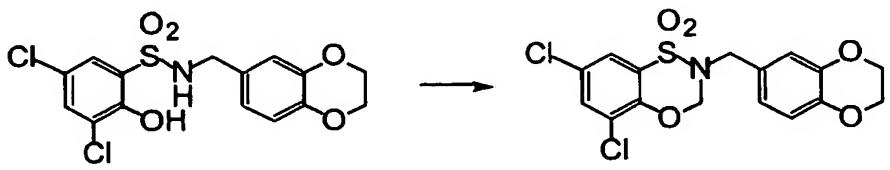
MS(EI)E/Z389(M^+),391(M+2),393(M+4)

Preparation Example 79

Synthesis of

5,7-dichloro-2-[(2,3-dihydro-1,4-benzodioxin-6-yl)methyl]-2,3-dihydro-4,1,2-benzoxathiazine-1,1-dioxide

A mixture of 439 mg (1.12 mmol) of BAK-KA254 obtained in Preparation Example 78, 214 mg (1.12 mmol) of p-toluenesulfonic acid monohydrate, 1.00 ml of dimethoxymethane, and 10.0 ml of toluene was heated to reflux for 14 hours. 2 mol/l of hydrochloric acid was added to the reaction solution, the mixture was extracted with ethyl acetate, and the resulting organic layer was washed with saturated brine. After drying over anhydrous magnesium sulfate and concentration, the resulting crude product was purified by silica gel column chromatography (hexane : ethyl acetate = 3 : 1) to obtain 416 mg (yield: 92%) of the title compound (BAK-KA255-1).



BAK-KA254 BAK-KA255-1

^{1}H-NMR($CDCl_3$)δ:

4.27 (s, 4H), 4.29 (s, 2H), 5.48 (s, 2H), 6.86-6.89 (m, 3H),

7.55 (d, J=2.5Hz, 1H), 7.67 (d, J=2.5Hz, 1H)

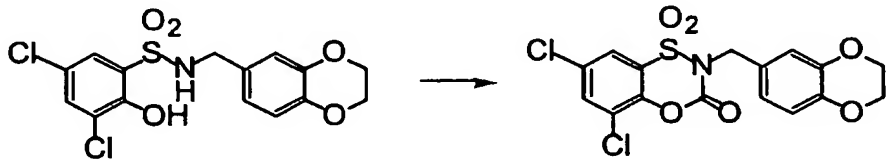
MS(EI)E/Z401(M^+),403(M+2),405(M+4)

Preparation Example 80

Synthesis of

5,7-dichloro-2-[(2,3-dihydro-1,4-benzodioxin-6-yl)methyl]-4,1,2-benzoxathiazin-3(2H)-one-1,1-dioxide

A mixture of 300 mg (0.77 mmol) of BAK-KA254 obtained in Preparation Example 78, 249 mg (1.53 mmol) of N,N-carbodiimidazole, 94.0 mg (0.77 mmol) of dimethylaminopyridine, and 5.00 ml of anhydrous dimethylformamide was stirred for 21 hours at room temperature. 2 mol/l of hydrochloric acid was added to the reaction solution, the mixture was extracted with ethyl acetate, and the resulting organic layer was washed with saturated aqueous solution of sodium hydrogencarbonate and saturated brine. After drying over anhydrous magnesium sulfate and concentration, the resulting crude product was purified by silica gel column chromatography (hexane : ethyl acetate = 4 : 1) to obtain 222 mg (yield: 69%) of the title compound (BAK-KA257).



BAK-KA254 BAK-KA257

^{1}H-NMR($CDCl_3$)δ:

4.23 (s, 4H), 4.94 (s, 2H), 6.82 (d, J=8.2Hz, 1H), 6.98 (dd, J=2.1, 8.2Hz, 1H), 7.00 (d, J=2.1Hz, 1H), 7.72 (d, J=2.4Hz, 1H), 7.75 (d, J=2.4Hz, 1H)

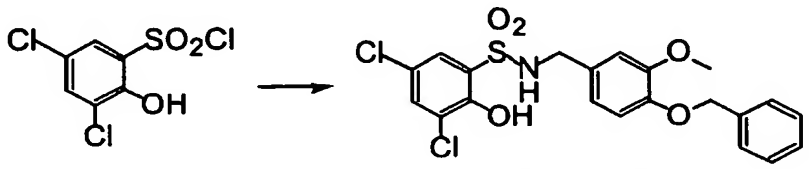
MS(EI)E/Z415(M^+),417(M+2),419(M+4)

Preparation Example 81

Synthesis of

N-[4-(benzyloxy)-3-methoxybenzyl)-3,5-dichloro-2-hydroxybenezenesulfonamide

The title compound (BAK-KA266) was obtained at a yield of 88% in the same manner as in Preparation Example 78.



BAK-KA266

^{1}H-NMR($CDCl_3$)δ:

4.09 (s, 3H), 4.13 (d, 2H), 5.08 (t, 1H), 5.12 (s, 2H), 6.61-6.78 (m, 3H), 7.31-7.53 (m, 7H)

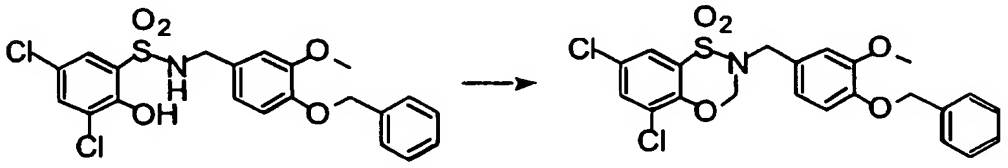
MS(EI)E/Z467(M^+),469(M+2),471(M+4)

Preparation Example 82

Synthesis of

2-[4-(benzyloxy)-3-methoxybenzyl]-5,7-dichloro-2,3-dihydro-4,1,2-benzoxathiazine-1,1-dioxide

The title compound (BAK-KA268-1) was obtained at a yield of 74% in the same manner as in Preparation Example 79.



BAK-KA266 BAK-KA268-1

^{1}H-NMR($CDCl_3$)δ:

3.90 (s, 3H), 4.32 (s, 2H), 5.17 (s, 2H), 5.47 (s, 2H), 6.86-6.91 (m, 3H),

7.31 (m, 7H)

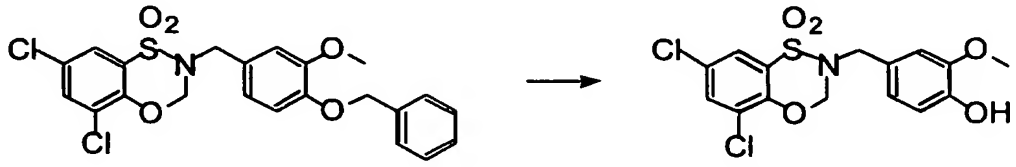
MS(EI)E/Z479(M^+),481(M+2),483(M+4)

Preparation Example 83

Synthesis of

5,7-dichloro-2,3-dihydro-2-(4-hydroxy-3-methoxybenzyl)-4,1,2-benzoxathiazine-1,1-dioxide

A mixture of 604 mg (1.22 mmol) of BAK-KA268-1 obtained in Preparation Example 82, 60.0 mg of 10% Pd-C, and 10.0 ml of ethyl acetate was stirred in a hydrogen stream for three hours at room temperature. Catalyst was separated by filtration and the filtrate was concentrated and recrystallized from methylene chloride-hexane to obtain 390 mg (yield: 82%) of the title compound (BAK-KA269).



BAK-KA268-1 BAK-KA269

^{1}H-NMR($CDCl_3$)δ:

3.91 (s, 3H), 4.32 (s, 2H), 5.48 (s, 2H), 5.69 (s, 1H), 6.85-6.94 (m, 3H), 7.56 (d, J=2.5Hz, 1H), 7.68 (t, J=2.5Hz, 1H)

MS(EI)E/Z389(M^+),391(M+2),393(M+4)

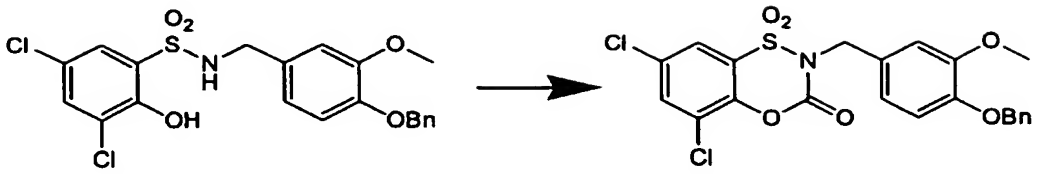
Preparation Example 84

Synthesis of

2-[4-(benzyloxy)-3-methoxybenzyl]-5,7-dichloro-4,1,2-benzoxathiazin-3(2H)-one-1,1-dioxide

The title compound (BAK-KA267) was obtained at a yield of 85% in the same

manner as in Preparation Example 80.



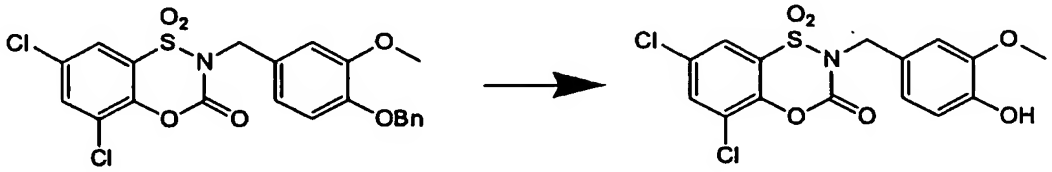
KA266 KA267

Preparation Example 85

Synthesis of

5,7-dichloro-2-(4-hydroxy-3-methoxybenzyl)-4,1,2-benzoxathiazin-3(2H)-one-1,1-dioxide

The title compound (BAK-KA271) was obtained at a yield of 42% in the same manner as in Preparation Example 83.



KA267 KA271

^{1}H-NMR($CDCl_3$)d:

3.89 (s, 3H), 4.98 (s, 2H), 5.66 (brs, 1H), 6.85-7.04 (m, 3H),

7.72 (d, J=2.4Hz, 1H), 7.74 (t, J=2.4Hz, 1H)

MS(EI)E/Z403(M^+),405(M+2),407(M+4)

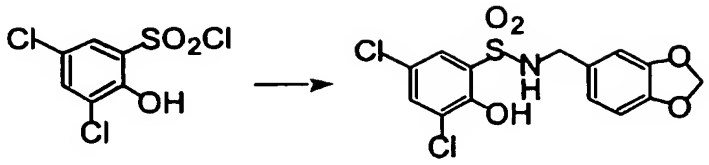
Preparation Example 86

Synthesis of

3,5-dichloro-2-hydroxy-N-[3,4-(methylenedioxy)benzyl]benzenesulfonamide

The title compound (BAK-KA275) was obtained at a yield of 78% in the same

manner as in Preparation Example 78.



BAK-KA275

^{1}H-NMR($CDCl_3$)δ:

4.10 (d, J=6.0Hz, 2H), 5.09 (t, J=6.0Hz, 1H), 5.94 (s, 2H), 6.59-6.71 (m, 3H), 7.52 (s, 2H), 8.34 (brs, 1H)

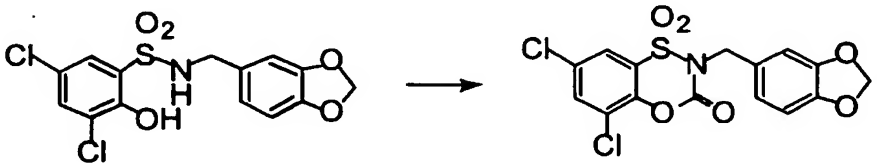
MS(EI)E/Z375(M^+),377(M+2),379(M+4)

Preparation Example 87

Synthesis of

5,7-dichloro-2-[3,4-(methylenedioxy)benzyl)-4,1,2-benzoxathiazin-3(2H)-one-1,1-dioxide

The title compound (BAK-KA277) was obtained at a yield of 82% in the same manner as in Preparation Example 80.



BAK-KA275 BAK-KA277

^{1}H-NMR($CDCl_3$)δ:

4.96 (s, 2H), 5.95 (s, 2H), 6.74-6.99 (m, 3H), 7.73 (d, J=2.4Hz, 1H), 7.75 (d, J=2.4Hz, 1H)

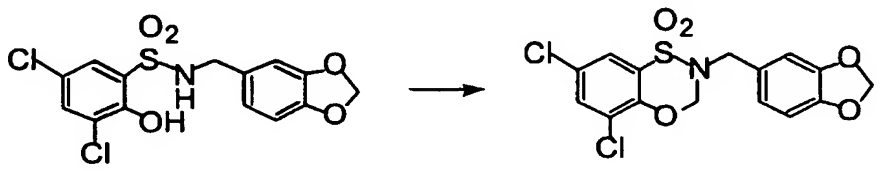
MS(EI)E/Z401(M^+),403(M+2),405(M+4)

Preparation Example 88

Synthesis of

5,7-dichloro-2,3-dihydro-2-[3,4-(methylenedioxy)benzyl]-4,1,2-benzoxathiazine-1,1-dioxide

The title compound (BAK-KA288) was obtained at a yield of 42% in the same manner as in Preparation Example 79.



BAK-KA275 BAK-KA288

^{1}H-NMR($CDCl_3$)δ:

4.31 (s, 2H), 5.48 (s, 2H), 5.99 (s, 2H), 6.78-6.88 (m, 3H),

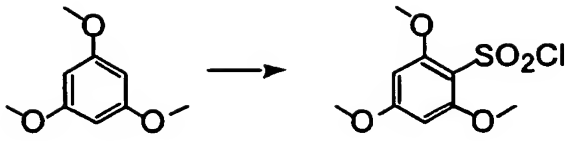
7.56 (d, J=2.5Hz, 1H), 7.67 (d, J=2.5Hz, 1H)

MS(EI)E/Z387(M^+),389(M+2),391(M+4)

Preparation Example 89

Synthesis of 2,4,6-trimethoxybenzenesulfonyl chloride

2.0 g (11.9 mmol) of phloroglucinol trimethyl ether was added in small amounts to 5.00 ml of chlorosulfonic acid. The mixture was stirred for 1.5 hour at room temperature and for one hour at 50°C. The reaction solution was carefully poured into 200 ml of ice and the mixture was extracted with chloroform. The resulting organic layer was dried over anhydrous magnesium sulfate. After concentration, the resulting crude product was purified by silica gel column chromatography (hexane : ethyl acetate = 4 : 1 → 1 :1) to obtain 1.23 g (yield: 39%) of the title compound (BAK-KA260-1).



BAK-KA260-1

^{1}H-NMR($CDCl_3$)δ:

2.89 (s, 3H), 3.96 (s, 6H), 6.12 (s, 2H)

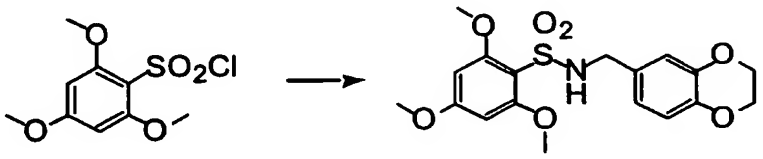
MS(EI)E/Z266(M^+)

Preparation Example 90

Synthesis of

N-[(2,3-dihydro-1,4-benzodioxin-6-yl)methyl]-2,4,6-trimethoxybenzenesulfonamide

The title compound (BAK-KA261) was obtained at a yield of 78% in the same manner as in Preparation Example 78.



BAK-KA260-1 BAK-KA261

^{1}H-NMR($CDCl_3$)δ:

3.85 (s, 9H), 4.02 (d, J=6.3Hz, 2H), 4.21 (s, 4H), 5.31 (t, J=6.3Hz, 1H),

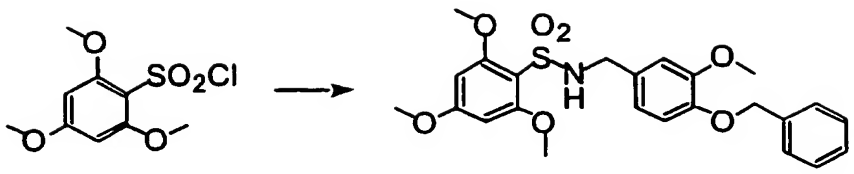
6.09 (s, 2H), 6.68-6.76 (m, 3H)

MS(EI)E/Z395(M^+)

Preparation Example 91

Synthesis of N-[4-(benzyloxy)-3-methoxybenzyl]-2,4,6-trimethoxybenzenesulfonamide

The title compound (BAK-KA290) was obtained at a yield of 86% in the same manner as in Preparation Example 78.



BAK-KA260-1 BAK-KA290

^{1}H-NMR($CDCl_3$)δ:

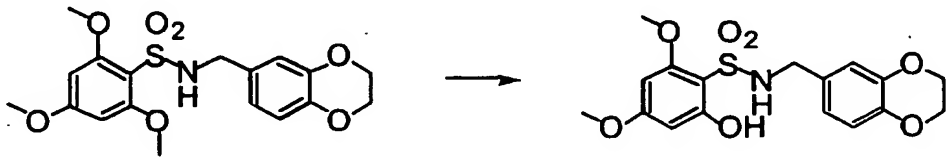
3.81 (s, 6H), 3.82 (s, 3H), 3.83 (d, J=3.7Hz, 2H), 3.84 (s, 3H), 5.12 (s, 2H), 5.32 (t, J=3.7Hz, 1H), 6.09 (s, 2H), 6.60-6.79 (m, 3H), 7.29-7.44 (m, 5H)

MS(EI)E/Z473(M^+)

Preparation Example 92

Synthesis of N-[(2,3-dihydro-1,4-benzodioxin-6-yl)methyl]-2-hydroxy-4,6-methoxybenzenesulfonamide

A mixture of 1.26 g (3.19 mmol) of BAK-KA261 obtained in Preparation Example 90, 2.13 g (15.9 mmol) of lithium iodide, and 30 ml of anhydrous dioxane was heated to reflux for 14 hours. Water was added to the reaction solution, the mixture was extracted with ethyl acetate, and the resulting organic layer was washed with saturated brine, followed by drying over anhydrous magnesium sulfate. After concentration, the residue was purified by silica gel column chromatography (hexane : ethyl acetate = 4 : 1 → 1 : 1) to obtain 946.5 mg (yield: 78%) of the title compound (BAK-KA262).



BAK-KA261 BAK-KA262

^{1}H-NMR($CDCl_3$)δ:

3.78 (s, 3H), 3.81 (s, 3H), 3.98 (d, 2H), 4.21 (s, 4H), 5.94 (d, J=2.2Hz, 1H),

6.11 (d, J=2.2Hz, 1H), 6.61-6.76 (m, 3H), 9.84 (s, 1H)

MS(EI)E/Z381(M^+)

Preparation Example 93

Synthesis of

2-[(2,3-dihydro-1,4-benzodioxin-6-yl)methyl]-2,3-dihydro-6,8-dimethoxy-4,1,2-benzoxathiazine-1,1-dioxide

A mixture of 436 mg (1.14 mmol) of BAK-KA262 obtained in Preparation Example 92, 10.0 ml of formalin aqueous solution, 0.50 ml of acetic acid, and 20 ml of anhydrous methanol was heated to reflux for 69.5 hours. 1 mol/l of aqueous solution of sodium hydroxide was added to the reaction solution, the mixture was extracted with ethyl acetate, and the resulting organic layer was washed with saturated brine. After drying over anhydrous magnesium sulfate and concentration, the residue was purified by silica gel column chromatography (hexane : ethyl acetate = 3 : 1 → chloroform) to obtain 272 mg (yield: 60%) of the title compound (BAK-KA264).

BAK-KA262 BAK-KA264

^{1}H-NMR($CDCl_3$)d:

3.81 (s, 3H), 3.94 (s, 3H), 4.27 (s, 4H), 4.34 (s, 2H), 5.24 (s, 2H),

6.09 (d, J=2.3Hz, 1H), 6.15 (d, J=2.3Hz, 1H), 6.87-6.93 (m, 3H)

MS(EI)E/Z393(M^+)

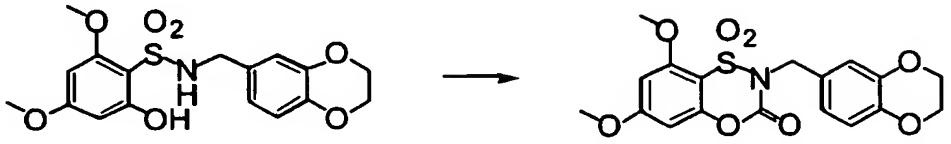
Preparation Example 94

Synthesis of

2-[(2,3-dihydro-1,4-benzodioxin-6-yl)methyl]-6,8-dimethoxy-4,1,2-benzoxathiazin-

3(2H)-one-1,1-dioxide

The title compound (BAK-KA265) was obtained at a yield of 87% in the same manner as in Preparation Example 80.



BAK-KA262 BAK-KA265

^{1}H-NMR($CDCl_3$)d:

3.85 (s, 3H), 3.97 (s, 3H), 4.22 (s, 4H), 4.92 (s, 2H), 6.32 (d, J=2.2Hz, 1H), 6.35 (d, J=2.2Hz, 1H), 6.80 (d, J=8.2Hz, 1H), 7.01 (dd, J=2.0, 8.2Hz, 1H), 7.06 (d, J=2.0Hz, 1H)

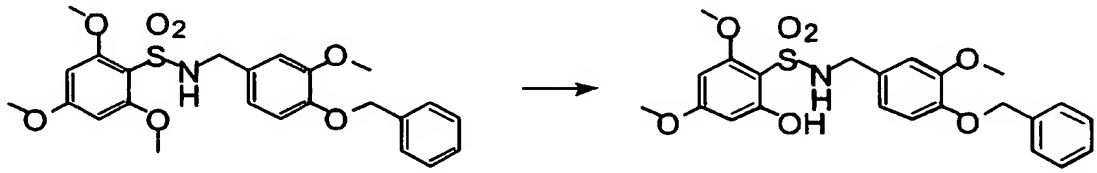
MS(EI)E/Z407(M^+)

Preparation Example 95

Synthesis of

N-[4-(benzyloxy)-3-methoxybenzyl]-2-hydroxy-4,6-dimethoxybenzenesulfonamide

2.20 g (quantitative yield) of the title compound (BAK-KA292) was obtained in the same manner as in Preparation Example 92.



BAK-KA290 BAK-KA292

^{1}H-NMR($CDCl_3$)δ:

3.68 (s, 3H), 3.80 (s, 3H), 3.83 (s, 3H), 4.03 (d, 2H), 5.12 (s, 2H), 5.90 (d, J=2.3Hz, 1H), 6.11 (d, J=2.3Hz, 1H), 6.57-6.77 (m, 3H), 7.29-7.45 (m, 5H), 9.86 (s, 1H)

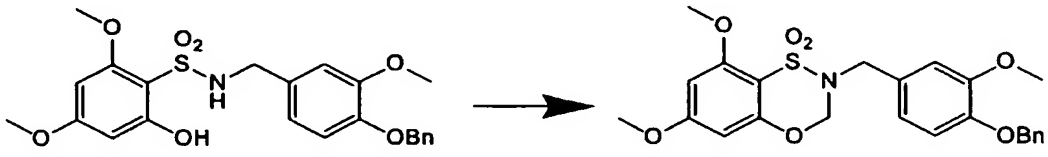
MS(EI)E/Z459(M^+)

Preparation Example 96

Synthesis of

2-[4-(benzyloxy)-3-methoxybenzyl]-2,3-dihydro-6,8-dimethoxy-4,1,2-benzoxathiazine-1,1-dioxide

A mixture of 1.00 g (2.18 mmol) of BAK-KA292 obtained in Preparation Example 95, 20.0 ml of formalin aqueous solution, 1.00 ml of acetic acid, and 20.0 ml of anhydrous methanol was heated to reflux for 19.5 hours. 10% aqueous solution of sodium hydroxide was added to the reaction solution, the mixture was extracted with ethyl acetate, and the resulting organic layer was washed with saturated brine. After drying over anhydrous magnesium sulfate and concentration, the residue was purified by silica gel column chromatography (hexane : ethyl acetate = 4 : 1 → 2 :1) to obtain 566 mg [yield: 55%) of the title compound (BAK-KA294).



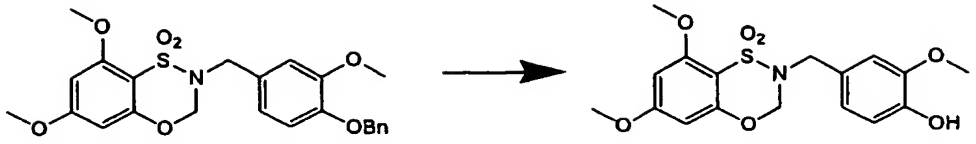
KA292 KA294

Preparation Example 97

Synthesis of

2,3-dihydro-2-(4-hydroxy-3-methoxybenzyl)-6,8-dimethoxy-4,1,2-benzoxathiazine-1,1-dioxide

The title compound (BAK-KA296) was obtained at a yield of 42% in the same manner as in Preparation Example 83.



KA294 KA296

^{1}H-NMR($CDCl_3$)δ:

3.81 (s, 3H), 3.91 (s, 3H), 3.95 (s, 3H), 4.37 (s, 2H), 5.23 (s, 2H), 5.66 (s, 1H), 6.10 (d, J=2.2Hz, 1H), 6.17 (d, J=2.2Hz, 1H), 6.84-6.94 (m, 3H)

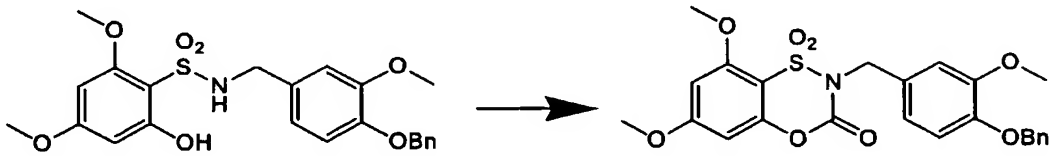
MS(EI)E/Z381(M^+)

Preparation Example 98

Synthesis of

2-[4-(benzyloxy)-3-methoxybenzyl]-6,8-dimethoxy-4,1,2-benzoxathiazin-3(2H)-one-1,1-dioxide

The title compound (BAK-KA295) was obtained in the same manner as in Preparation Example 80.



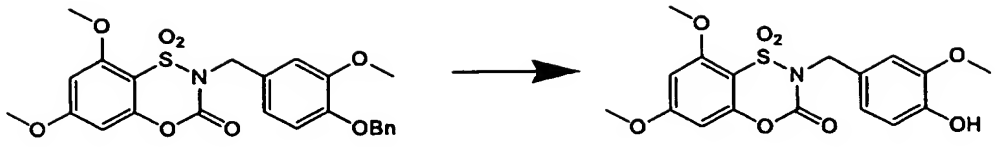
KA292 KA295

Preparation Example 99

Synthesis of

6,8-dimethoxy-2-(4-hydroxy-3-methoxybenzyl)-4,1,2-benzoxathiazin-3(2H)-one-1,1-dioxide

The title compound (BAK-KA297) was obtained at a yield of 18% in the same manner as in Preparation Example 83.



KA295 KA297

^{1}H-NMR($CDCl_3$)δ:

3.85 (s, 3H), 3.88 (s, 3H), 3.98 (s, 3H), 4.95 (s, 2H), 5.61 (s, 1H),

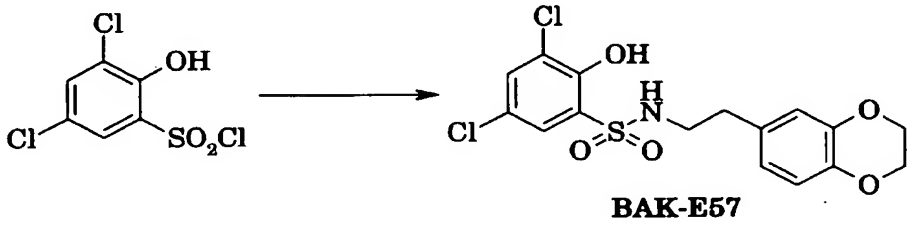
6.32 (d, J=2.2Hz, 1H), 6.36 (t, J=2.2Hz, 1H), 6.83-7.10 (m, 3H)

MS(EI)E/Z395(M^+)

Preparation Example 100

Synthesis of 3,5-dichloro-N-[2-(2,3-dihydro-1,4-benzodioxin-6-yl)ethyl]-2-hydroxybenzenesulfonamide

The title compound (BAK-E57) was obtained at a yield of 78% in the same manner as in the Preparation Example 78.



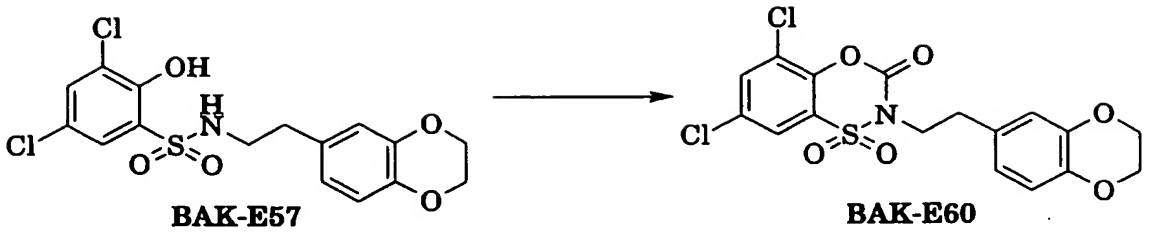
BAK-E57

Preparation Example 101

Synthesis of

6,8-dichloro-2-[2-(2,3-dihydro-1,4-benzodioxin-6-yl)ethyl]-4,1,2-benzoxathiazin-3(2H)-one

The title compound (BAK-E60) was obtained at a yield of 47% in the same manner as in the Preparation Example 80.



^{1}H-NMR($CDCl_3$)δ:

2.92-3.00 (m, 2H), 4.03-4.14 (m, 2H), 4.22 (s, 4H),

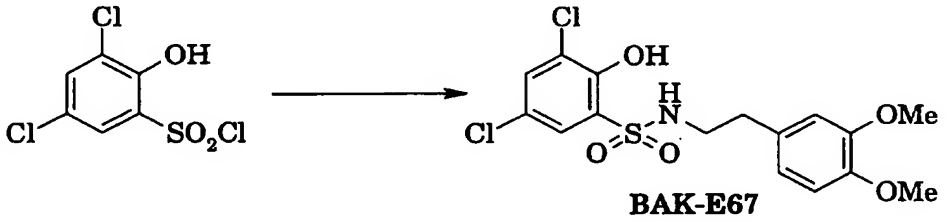
6.65 (dd, J=2.0, 8.5Hz, 1H), 6.67 (d, J=2.0Hz, 1H), 6.74 (d, J=8.5Hz, 1H),

7.69 (d, J=2.4Hz, 1H), 7.74 (d, J=2.4Hz, 1H)

Preparation Example 102

Synthesis of 3,5-dichloro-N-(3,4-dimethoxyphenethyl)-2-hydroxybenzenesulfonamide

The title compound (BAK-E67) was obtained at a yield of 86% in the same manner as in the Preparation Example 78.



^{1}H-NMR($CDCl_3$)δ:

2.73 (t, J=6.6Hz, 2H), 3.28 (t, 6.6Hz, 2H), 3.84 (s, 3H), 3.86 (s, 3H),

6.57 (d, J=2.0Hz, 1H), 6.61 (dd, J=2.0, 8.0Hz, 1H), 6.78 (d, J=8.0Hz, 1H),

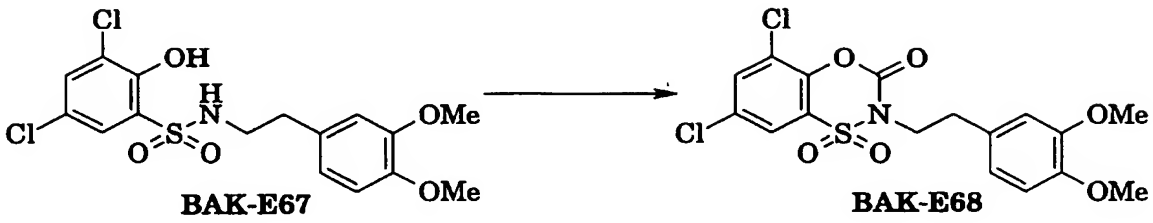
7.51 (d, J=2.5Hz, 1H), 7.53 (d, J=2.5Hz, 1H).

MS(EI)E/Z405(M^+).

Preparation Example 103

Synthesis of 5,7-dichloro-2-(3,4-dimethoxyphenethyl)-4,1,2-benzoxathiazin-3(2H)-one

The title compound (BAK-E68) was obtained at a yield of 93% in the same manner as in the Preparation Example 80.



^{1}H-NMR($CDCl_3$)δ:

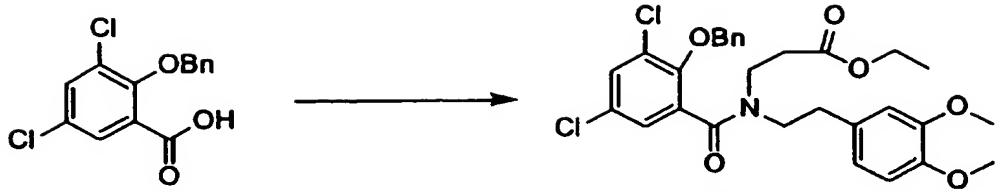
3.03 (m, 2H), 3.84 (s, 3H), 3.86 (s, 3H), 4.12 (m, 2H), 6.70 (s, 1H), 6.72 (s, 2H), 7.65 (d, J=2.4Hz, 1H), 7.73 (d, J=2.4Hz, 1H)

MS(EI)E/Z431(M^+)

Preparation Example 104

Synthesis of ethyl 3-[N-(2-benzyloxy-3,5-dichlorobenzoyl)-N-(3,4-dimethoxyphenethyl)amino]propionate

0.41 ml (2.7 mmol) of DEPC was added to a mixture of 667.3 mg (2.25 mmol) of 2-benzyloxy-3,5-dichlorobenzoic acid, 681 mg (2.25 mmol) of ethyl 3-[[2-(3,4-dimethoxyphenyl)ethyl]amino]propanoate hydrochloride, 0.94 ml (5.4 mmol) of DIEA, and 13 ml of DMF. The mixture was stirred for two hours at room temperature. Water was added to the reaction solution, the mixture was extracted with ethyl acetate, and the resulting organic layer was dried over anhydrous sodium sulfate. After concentration, the resulting crude product was purified by silica gel column chromatography (hexane : ethyl acetate = 2 : 1) to obtain 1.27 g (yield: 100%) of the title compound (BAK-G492).



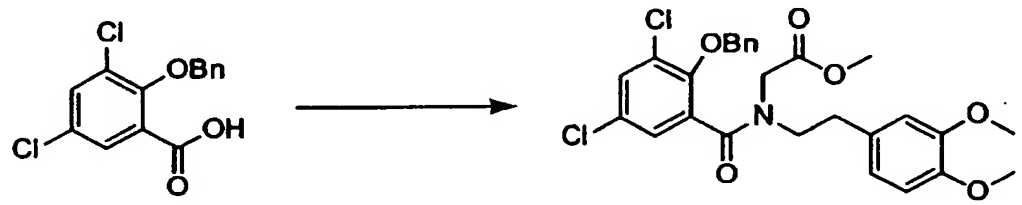
BAK-G484 **BAK-G492**

MS(EI)E/Z559(M^+).

Preparation Example 105

Synthesis of methyl [N-(2-benzyloxy-3,5-dichlorobenzoyl)-N-(3,4-dimethoxyphenethyl)amino]acetate

The title compound (BAK-G494) was obtained at a yield of 99% in the same manner as in the Preparation Example 104.



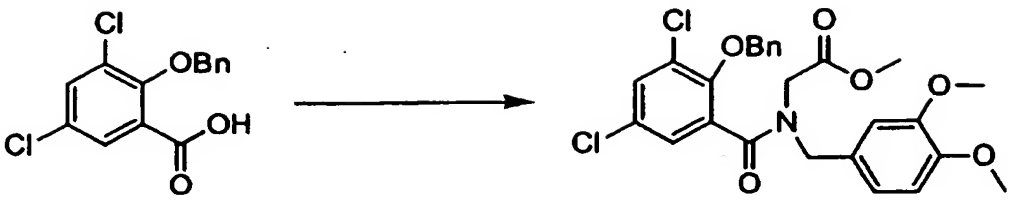
BAK-G484 **BAK-G494**

MS(EI)E/Z531(M^+).

Preparation Example 106

Synthesis of methyl [N-(2-benzyloxy-3,5-dichlorobenzoyl)-N-(3,4-dimethoxybenzyl)amino]acetate

The title compound (BAK-G499) was obtained at a yield of 73% in the same manner as in the Preparation Example 104.



BAK-G484 **BAK-G499**

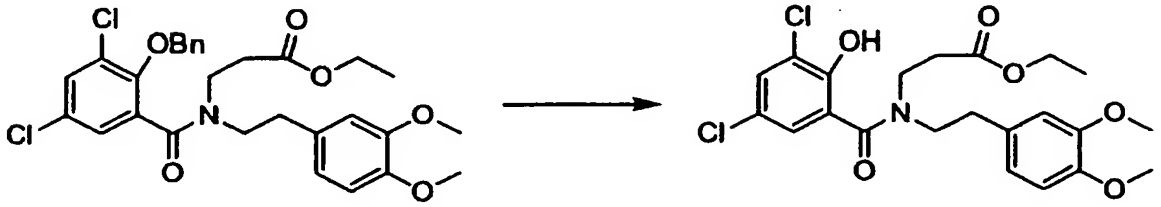
MS(EI)E/Z517(M^+).

Preparation Example 107

Synthesis of ethyl

3-[N-(3,5-dichloro-2-hydroxybenzoyl)-N-(3,4-dimethoxyphenethyl)amino]propionate

The title compound (BAK-G493) was obtained at a yield of 91% in the same manner as in the Preparation Example 66.



BAK-G492 **BAK-G493**

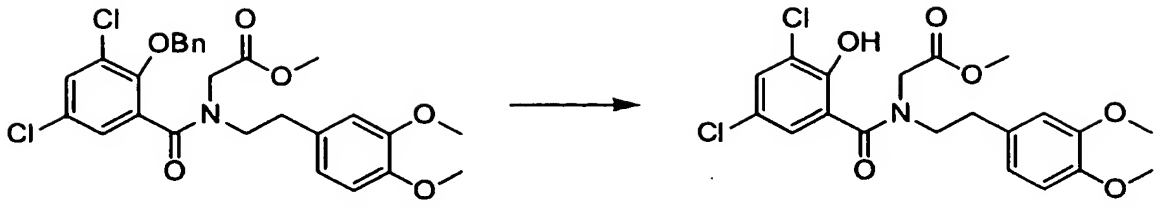
MS(EI)E/Z469(M^+).

Preparation Example 108

Synthesis of methyl

[N-(3,5-dichloro-2-hydroxybenzoyl)-N-(3,4-dimethoxyphenethyl)amino]acetate

The title compound (BAK-G495) was obtained at a yield of 91% in the same manner as in the Preparation Example 66.



BAK-G494 **BAK-G495**

^{1}H-NMR($CDCl_3$)δ:

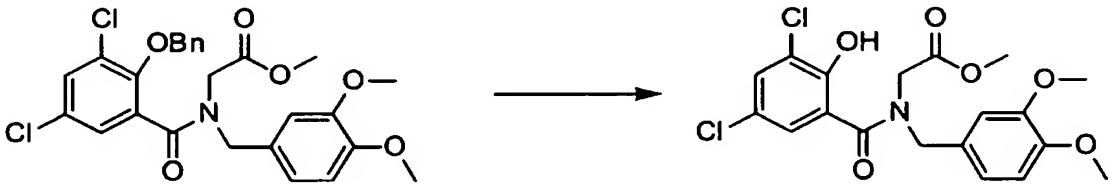
2.81 (t, J=7.0Hz, 2H), 3.62 (t, J=7.0Hz, 2H), 3.81 (s, 3H), 3.82 (s, 3H), 3.87 (s, 3H), 4.19 (s, 2H), 6.50-6.65 (m, 2H), 6.75-6.85 (m, 2H), 7.37 (d, J=2.5Hz, 1H)

MS(EI)E/Z441(M^+)

Preparation Example 109

Synthesis of methyl [N-(3,5-dichloro-2-hydroxybenzoyl)-N-(3,4-dimethoxybenzyl)amino]acetate

The title compound (BAK-G500) was obtained at a yield of 90% in the same manner as in the Preparation Example 66.



BAK-G499 **BAK-G500**

^{1}H-NMR($CDCl_3$)δ:

3.78 (s, 3H), 3.87 (s, 3H), 3.89 (s, 3H), 4.10 (s, 2H), 4.64 (s, 2H), 6.70-6.90 (m, 3H), 7.26 (d, J=2.5Hz, 1H), 7.43 (d, J=2.5Hz, 1H).

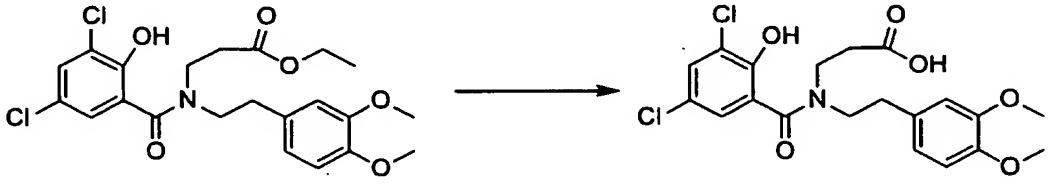
MS(EI)E/Z427(M^+).

Preparation Example 110

Synthesis of

3-[N-(3,5-dichloro-2-hydroxybenzoyl)-N-(3,4-dimethoxyphenethyl)amino]propionic acid

The title compound (BAK-G497) was obtained at a yield of 98% in the same manner as in the Preparation Example 68.



BAK-G493 BAK-G497

^{1}H-NMR($CDCl_3$)δ:

2.65-2.85 (m, 4H), 3.59 (m, 2H), 3.79 (m, 2H), 3.80 (s, 3H), 3.87 (s, 3H), 6.45-6.60 (m, 2H), 6.75-6.80 (m, 2H), 7.31 (d, J=2.5Hz, 1H)

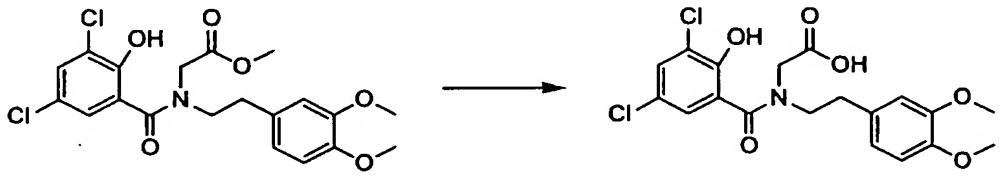
MS(EI)E/Z441(M^+)

Preparation Example 111

Synthesis of

[N-(3,5-dichloro-2-hydroxybenzoyl)-N-(3,4-dimethoxyphenethyl)amino]acetic acid

The title compound (BAK-G496) was obtained at a yield of 100% in the same manner as in the Preparation Example 68.



BAK-G495 BAK-G496

^{1}H-NMR($CDCl_3$)δ:

2.81 (t, J=6.7Hz, 2H), 3.62 (t, J=6.7Hz, 2H), 3.82 (s, 3H), 3.87 (s, 3H), 4.22 (s, 2H), 6.50-6.65 (m, 2H), 6.75-6.85 (m, 2H), 7.37 (d, J=2.5Hz, 1H)

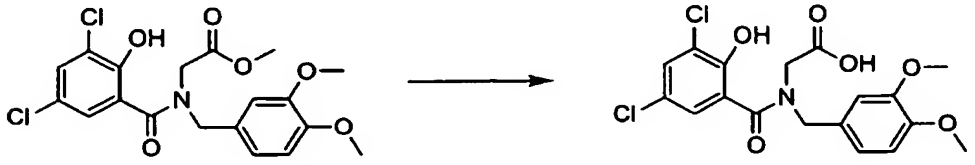
MS(EI)E/Z427(M^+)

Preparation Example 112

Synthesis of

[N-(3,5-dichloro-2-hydroxybenzoyl)-N-(3,4-dimethoxybenzyl)amino]acetic acid

The title compound (BAK-G501) was obtained at a yield of 100% in the same manner as in the Preparation Example 68.



BAK-G500 BAK-G501

^{1}H-NMR($CDCl_3$)δ:

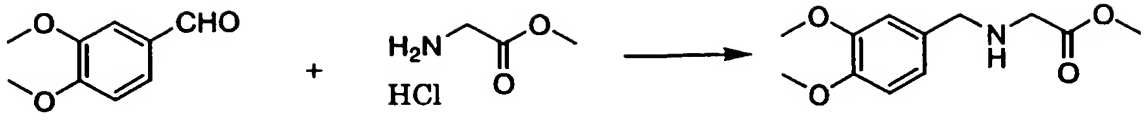
3.87 (s, 3H), 3.89 (s, 3H), 4.14 (s, 2H), 4.63 (s, 2H), 6.70-6.90 (m, 3H), 7.26 (d, J=2.5Hz, 1H), 7.43 (d, J=2.5Hz, 1H)

MS(EI)E/Z413(M^+)

Preparation Example 113

Synthesis of methyl [(3,4-dimethoxybenzyl)amino]acetate

A mixture of 1.66 g (10.0 mmol) of 3,4-dimethoxybenzaldehyde, 1.38 g (11.0 mmol) of glycine methyl ester hydrochloride, 1.6 ml (11.4 mmol) of triethylamine, 4.2 g (19.8 mmol) of sodium triacetoxy hydroboride, and 80 ml of methylene chloride was stirred for five hours at room temperature. Saturated aqueous solution of sodium hydrogencarbonate was added to the reaction solution and the mixture was extracted with chloroform. The resulting organic layer was dried over anhydrous magnesium sulfate. After concentration, the resulting crude product was purified by silica gel column chromatography (hexane : ethyl acetate = 1 : 1 → chloroform : methanol = 30 : 1) to obtain 2.27 g (yield: 95%) of the title compound (BAK-KA316).



BAK-KA316

^{1}H-NMR($CDCl_3$)δ:

3.42 (s, 3H), 3.91 (s, 3H), 3.74 (s, 2H), 3.87 (s, 3H), 3.89 (s, 3H),

6.83-6.89 (m, 3H)

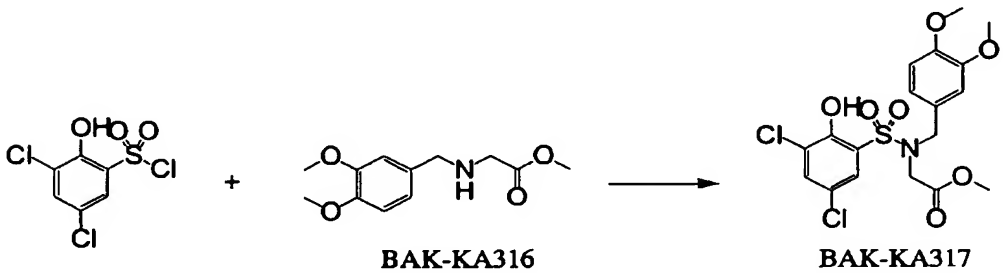
MS(EI)E/Z239(M)

Preparation Example 114

Synthesis of methyl

[[(3,5-dichloro-2-hydroxyphenyl)sulfonyl](3,4-dimethoxybenzyl)amino]acetate

A mixture of 2.22 g (8.52 mmol) of 3,5-benzenesulfonyl chloride, 2.04 g (8.52 mmol) of BAK-KA316 obtained in Preparation Example 113, 3.57 ml (25.6 mmol) of triethylamine, and 85 ml of chloroform was stirred for 17.5 hours at room temperature. 1 mol/l of hydrochloric acid was added to the reaction solution and the mixture was extracted with chloroform. The resulting organic layer was washed with saturated aqueous solution of sodium hydrogencarbonate and saturated brine and dried over anhydrous magnesium sulfate. After concentration, the resulting crude product was purified by silica gel column chromatography (hexane : ethyl acetate = 1 : 1) to obtain 3.28 g (yield: 83%) of the title compound (BAK-KA317).



BAK-KA316 BAK-KA317

^{1}H-NMR($CDCl_3$)δ:

3.67 (s, 3H), 3.84 (s, 3H), 3.87 (s, 3H), 3.98 (s, 2H), 4.37 (s, 2H),

6.74-6.81 (m, 3H), 7.58 (d, J=1.5Hz, 1H), 7.66 (d, J=1.5Hz, 1H)

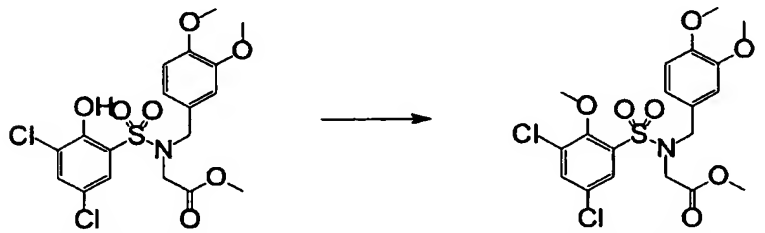
MS(EI)E/Z463(M),465(M+2)

Preparation Example 115

Synthesis of methyl

[[(3,5-dichloro-2-methoxyphenyl)sulfonyl](3,4-dimethoxybenzyl)amino]acetate

A mixture of 929 mg (2.00 mmol) of BAK-KA317 obtained in Preparation Example 114, 0.29 ml (2.2 mmol) of dimethylformamidedimethylacetal, and 0.7 ml of dimethylformamide was stirred for one hour at 110°C. 1 mol/l of hydrochloric acid was added to the reaction solution and the mixture was extracted with ethyl acetate. The resulting organic layer was washed with saturated aqueous solution of sodium hydrogencarbonate and saturated brine and dried over anhydrous magnesium sulfate. After concentration, the resulting crude product was purified by silica gel column chromatography (hexane : ethyl acetate = 2 : 1) to obtain 692 mg (yield: 72%)of the title compound (BAK-KA319).



BAK-KA317 BAK-KA319

^{1}H-NMR($CDCl_3$)δ:

3.62 (s, 3H), 3.82 (s, 3H), 3.99 (s, 2H), 4.01 (s, 3H), 4.52 (s, 2H),

6.75 (m, 3H), 7.57 (d, J=2.6Hz, 1H), 7.79 (d, J=2.6Hz, 1H)

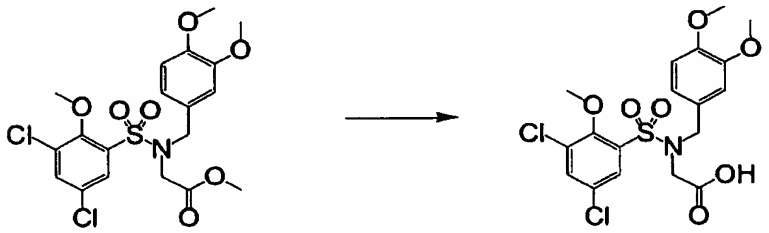
MS(EI)E/Z477(M),479(M+2)

Preparation Example 116

Synthesis of

[[(3,5-dichloro-2-methoxyphenyl)sulfonyl](3,4-dimethoxybenzyl)amino]acetic acid

A mixture of 692 mg (1.45 mmol) of BAK-KA319 obtained in Preparation Example 115, 174 mg (4.35 mmol) of sodium hydroxide, 5 ml of methanol, and 5 ml of water was stirred for 15 hours at room temperature. 1 mol/l of hydrochloric acid was added to the reaction solution and the mixture was extracted with chloroform. The resulting organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate. After concentration, the resulting crude product was recrystallized from methylene chloride-hexane to obtain 350 mg (yield: 52%) of the title compound (BAK-KA320).



BAK-KA319 BAK-KA320

^{1}H-NMR($CDCl_3$)δ:

3.81 (s, 3H), 3.86 (s, 3H), 4.03 (s, 3H), 4.06 (s, 2H), 4.49 (s, 2H),

6.71-6.76 (m, 3H), 7.57 (d, J=2.6Hz, 1H), 7.79 (d, J=2.6Hz, 1H)

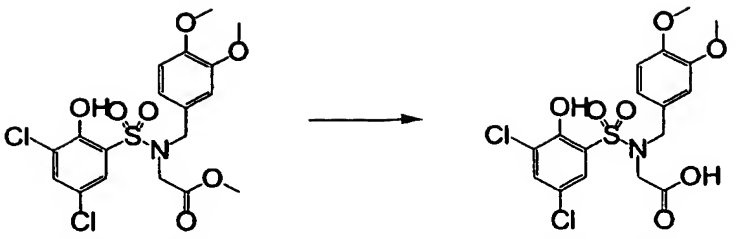
MS(EI)E/Z463(M),465(M+2)

Preparation Example 117

Synthesis of

[[(3,5-dichloro-2-hydroxyphenyl)sulfonyl](3,4-dimethoxybenzyl)amino]acetic acid

The title compound (BAK-KA323) was obtained at a yield of 53% in the same manner as in Preparation Example 116.



BAK-KA317 BAK-KA323

^{1}H-NMR($CDCl_3$)δ:

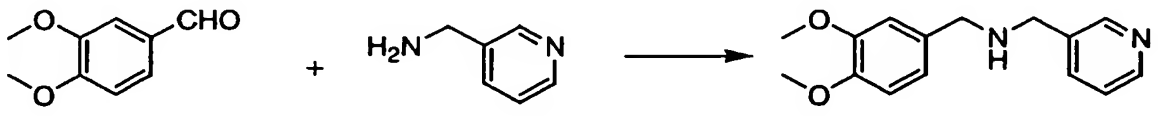
3.83 (s, 3H), 3.87 (s, 3H), 4.04 (s, 2H), 4.38 (s, 2H), 6.72-6.78 (m, 3H), 7.57 (d, J=2.5Hz, 1H), 7.79 (d, J=2.5Hz, 1H)

MS(EI)E/Z449(M),451(M+2)

Preparation Example 118

Synthesis of N-(3,4-dimethoxybenzyl)-1-(3-pyridinyl)methanamine

A mixture of 5.00 g (30.0 mmol) of 3,4-dimethoxybenzaldehyde, 3.1 ml (30.4 mmol) of 3-aminomethylpyridine, 5 g of anhydrous magnesium sulfate, and 20 ml of anhydrous diethylethel was stirred for three hours at room temperature. Magnesium sulfate was removed from the reaction solution by filtration. After concentration, 1.1 g (29.0 mmol) of sodium tetrahydroboride was added to the resulting reaction product and the mixture was stirred for three hours at room temperature. Saturated aqueous solution of sodium hydrogencarbonate was added to the reaction solution, the mixture was extracted with ethyl acetate, and the resulting organic layer was dried over anhydrous magnesium sulfate. After concentration, the resulting crude product was purified by silica gel column chromatography (hexane : ethyl acetate = 1 : 1 → chloroform : methanol = 20 : 1) to obtain 4.59 g (yield: 59%) of the title compound (BAK-KA331-2).



BAK-KA331-2

^{1}H-NMR($CDCl_3$)δ:

3.75 (s, 2H), 3.81 (s, 2H), 3.88 (s, 3H), 3.89 (s, 3H), 6.84-6.89 (m, 3H),

7.27 (dd, J=4.8, 7.8Hz, 1H), 7.69 (ddd, J=1.7, 2.0, 7.8Hz, 1H),

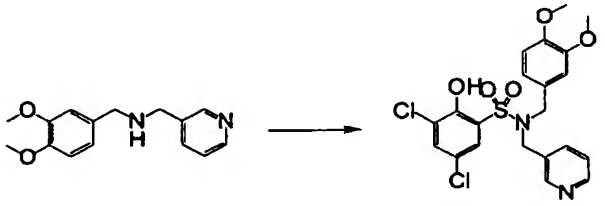
8.51 (dd, J=1.7, 4.8Hz, 1H), 8.58 (d, J=2.0Hz, 1H)

MS(EI)E/Z258(M)

Preparation Example 119

Synthesis of 3,5-dichloro-N-(3,4-dimethoxybenzyl)-2-hydroxy-N-[(3-pyridinyl)methyl] benzenesulfonamide

A mixture of 506 mg (1.94 mmol) of 3,5-benzenesulfonyl chloride, 500 mg (1.94 mmol) of BAK-KA331-2 obtained in Preparation Example 118, 0.8 ml (5.73 mmol) of triethylamine, and 20 ml of chloroform was stirred for 15 hours at room temperature. Saturated aqueous solution of sodium hydrogencarbonate was added to the reaction solution, the mixture was extracted with chloroform, and the resulting organic layer was dried over anhydrous sodium sulfate. After concentration, the crude product was purified by silica gel column chromatography (chloroform : methanol = 20 : 1) and recrystallized from methylene chloride-hexane-ethanol to obtain 683 mg (yield: 73%) of the title compound BAK-KA337.



BAK-KA331-2 BAK-KA337

Molecular weight: 483.365 ($C_{21}H_{20}Cl_2N_2O_5S$)

Melting point: 147-148°C (recrystallization from CH_2Cl_2-hexane-EtOH)

^{1}H-NMR($CDCl_3$)δ:

3.74 (s, 3H), 3.85 (s, 3H), 4.31 (s, 2H), 4.39 (s, 2H), 5.30 (s, 1H),

6.51-6.75 (m, 3H), 7.49-7.57 (m, 3H), 8.34 (d, 1H), 8.52 (dd, 1H)

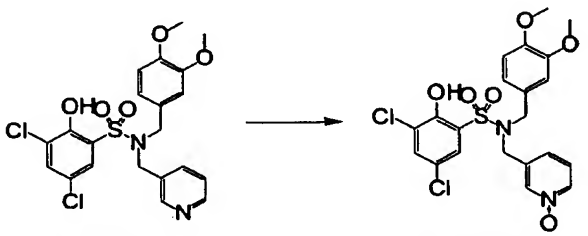
MS(EI)E/Z482(M),484(M+2)

Preparation Example 120

Synthesis of

3-[[[(3,5-dichloro-2-hydroxyphenyl)sulfonyl](3,4-dimethoxybenzyl)amino]methyl] pyridin-1-oxide

A mixture of 300 mg (0.66 mmol) of BAK-KA337 obtained in Preparation Example 119, 114 mg (0.97 mmol) of m-CPBA, and 12 ml of methylene chloride was stirred for 3.5 hours at room temperature. Saturated aqueous solution of sodium hydrogencarbonate was added to the reaction solution, the mixture was extracted with chloroform, and the resulting organic layer was dried over anhydrous magnesium sulfate. After concentration, the resulting crude product was recrystallized from methylene chloride-hexane-methanol to obtain 244 mg (yield: 79%) of the title compound (BAK-KA341).



BAK-KA337 BAK-KA341

^{1}H-NMR($CDCl_3$)δ:

3.71 (s, 3H), 3.83 (s, 3H), 4.24 (s, 2H), 4.42 (s, 2H), 6.51-6.69 (m, 3H), 7.20 (d, 2H), 7.57 (d, J=2.5Hz, 1H), 7.69 (d, J=2.5Hz, 1H), 8.10 (m, 1H), 8.28 (s, 1H)

MS(EI)E/Z482(M-O)

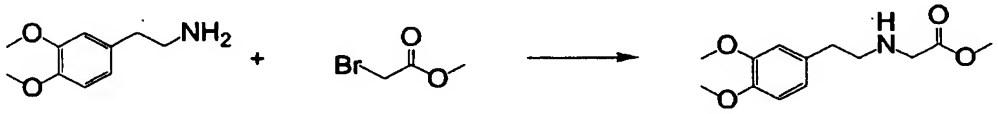
MS(FAB) +FAB499.1(M+1),

-FAB497.0(M-1)

Preparation Example 121

Synthesis of methyl [[2-(3,4-dimethoxyphenyl)ethyl]amino]acetate

A mixture of 3.38 ml (20.0 mmol) of 3,4-dimethoxyphenethylamine, 1.9 ml (20.0 mmol) of methyl 2-bromoacetate, 3.48 (20.0 mmol) of diisopropylethylamine, and 240 ml of anhydrous acetonitrile was stirred for 24 hours at 80 °C. After concentration of the reaction solution, the resulting crude product was purified by silica gel column chromatography (hexane : ethyl acetate = 1 : 1 → chloroform : methanol = 30 : 1) to obtain 3.89 g (yield: 77%) of the title compound (BAK-KA348).



BAK-KA348

^{1}H-NMR($CDCl_3$)δ:

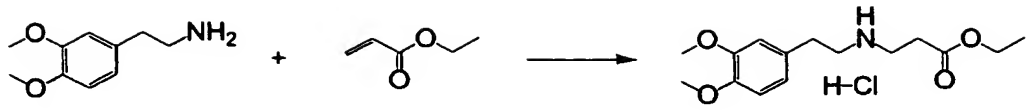
2.72-2.91 (m, 4H), 3.43 (s, 2H), 3.71 (s, 3H), 3.86 (s, 3H), 3.88 (s, 3H), 6.74-6.83 (m, 3H)

MS(EI)E/Z253(M)

Preparation Example 122

Synthesis of ethyl 3-[[2-(3,4-dimethoxyphenyl)ethyl]amino]propanoate hydrochloride

A mixture of 3.00 ml (17.2 mmol) of 3,4-dimethoxyphenethylamine, 1.86 ml (17.2 mmol) of ethyl acrylate, and 5.00 ml of anhydrous ethanol was stirred for two hours at room temperature. 2.0 ml of concentrated hydrochloric acid was added to the reaction solution and the mixture was recrystallized from acetone-diethylethel. The crystals were collected by filtration and washed with diethyl ether to obtain 4.24 g (yield: 81%) of the title compound (BAK-KA350).



BAK-KA350

^{1}H-NMR(DMSO-d_6)δ:

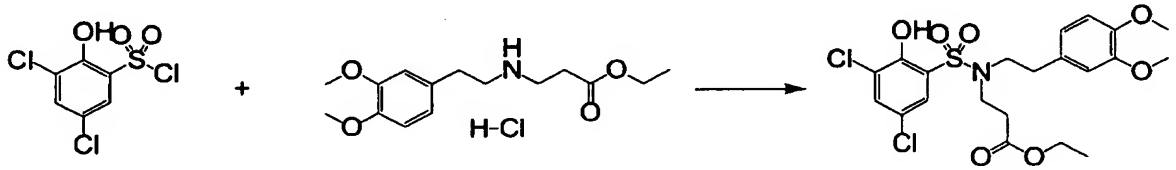
1.21 (t, J=7.1Hz, 3H), 2.75-2.91 (m, 4H), 3.14 (m, 4H), 3.72 (s, 3H), 3.75 (s, 3H), 4.11 (q, J=7.1Hz, 2H), 6.75-6.92 (m, 3H), 9.02 (brs, 2H)

MS(EI)E/Z279(M-HCl)

Preparation Example 123

Synthesis of ethyl 3-[[(3,5-dichloro-2-hydroxyphenyl]sulfonyl][(3,4-dimethoxyphenyl)ethyl]amino] propionate

A mixture of 500 mg (2.89 mmol) of 3,5-benzenesulfonyl chloride, 878 mg (2.89 mmol) of BAK-KA350 obtained in Preparation Example 122, 1.2 ml (8.59 mmol) of triethylamine, and 30 ml of chloroform was stirred for 1.5 hour at room temperature. 1 mol/l of hydrochloric acid was added to the reaction solution and the mixture was extracted with chloroform. The resulting organic layer was washed with saturated aqueous solution of sodium hydrogencarbonate and saturated brine and dried over anhydrous magnesium sulfate. After concentration, the resulting crude product was purified by silica gel column chromatography (hexane : ethyl acetate = 1 : 1) to obtain 942 mg (yield: 64%) of the title compound (BAK-KA352).



BAK-KA350 BAK-KA352

^{1}H-NMR($CDCl_3$)δ:

1.27 (t, J=7.1Hz, 3H), 2.62 (t, J=7.0Hz, 2H), 2.78 (t, J=8.1Hz, 2H),

3.46 (t, J=8.1Hz, 2H), 3.56 (t, J=7.1Hz, 2H), 3.86 (s, 3H), 3.87 (s, 3H),

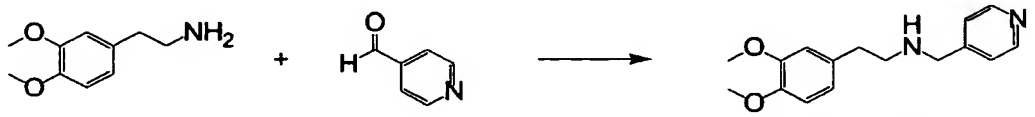
4.15 (q, J=7.1Hz, 2H), 7.43 (d, J=2.5Hz, 1H), 7.53 (d, J=2.5Hz, 1H)

MS(EI)E/Z505(M),507(M+2)

Preparation Example 124

Synthesis of 2-(3,4-dimethoxyphenyl)-N-[(4-pyridinyl)methyl]ethanamine

A mixture of 2.5 ml (26.8 mmol) of pyridine-4-carboxyaldehyde, 4.50 ml (26.8 mmol) of 3,4-dimethoxyphenethylamine, 1.35 g (21.5 mmol) of sodium cyanotrihydroboride, and 400 ml of anhydrous methanol was stirred for 17 hours at room temperature. After concentration, saturated aqueous solution of sodium hydrogencarbonate was added to the reaction solution and the mixture was extracted with ethyl acetate. The resulting organic layer was washed with saturated brine and dried over anhydrous sodium sulfate. After concentration, the crude product was purified by silica gel column chromatography (chloroform : methanol = 40 : 1 → 20 : 1) to obtain 3.78 g (yield: 52%) of the title compound (BAK-KA353-2).



BAK-KA353-2

^{1}H-NMR($CDCl_3$)δ:

2.78-2.89 (m, 4H), 3.81 (s, 2H), 3.87 (s, 6H), 6.70-6.84 (m, 3H),

7.21 (d, J=6.0Hz, 2H), 8.53 (d, J=6.0Hz, 2H)

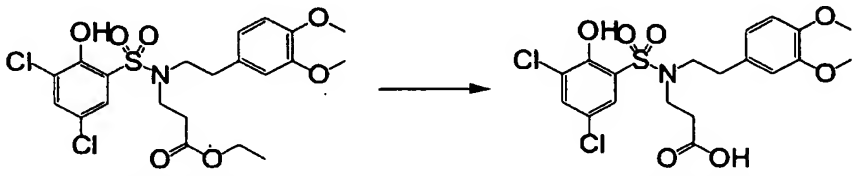
MS(EI)E/Z272(M)

Preparation Example 125

Synthesis of

3-[[(3,5-dichloro-2-hydroxyphenyl)sulfonyl][(3,4-dimethoxyphenyl)ethyl]amino] propionic acid

A mixture of 529 mg (1.04 mmol) of BAK-KA352 obtained in Preparation Example 123, 3.00 ml of concentrated hydrochloric acid, 6.00 ml of formic acid, and 3.00 ml of water was stirred for three hours at room temperature and further stirred for 2.5 hours at 60 °C. 1 mol/l of hydrochloric acid was added to the reaction solution, the mixture was extracted with chloroform, and the resulting organic layer was dried over anhydrous magnesium sulfate. After concentration, the resulting crude product was recrystallized from methylene chloride-hexane to obtain 364 mg (yield: 73%) of the title compound (BAK-KA354).



BAK-KA352 BAK-KA354

^{1}H-NMR($CDCl_3$)δ:

2.68 (t, J=7.0Hz, 2H), 2.79 (t, J=7.2Hz, 2H), 3.47 (t, J=7.2Hz, 2H), 3.55 (t, J=7.0Hz, 2H), 3.86 (s, 6H), 6.64-6.81 (m, 3H), 7.44 (d, J=2.5Hz, 1H), 7.54 (d, J=2.5Hz, 1H)

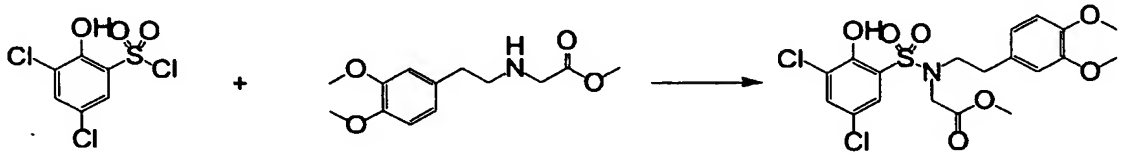
MS(EI)E/Z477(M),479(M+2)

Preparation Example 126

Synthesis of methyl [[(3,5-dichloro-2-hydroxyphenyl)sulfonyl][(3,4-dimethoxyphenyl)ethyl]amino]acetate

A mixture of 500 mg (2.89 mmol) of 3,5-benzenesulfonyl chloride, 732 mg (2.89 mmol) of BAK-KA348 obtained in Preparation Example 121, 1.2 ml (8.59 mmol) of triethylamine, and 30 ml of chloroform was stirred for one hour at room temperature. 1 mol/l of hydrochloric acid was added to the reaction solution and the mixture was extracted with chloroform. The resulting organic layer was washed with saturated aqueous solution of sodium hydrogencarbonate and saturated brine and dried over

anhydrous sodium sulfate. After concentration, the resulting crude product was purified by silica gel column chromatography (hexane : ethyl acetate = 1 : 1) to obtain 762 mg (yield: 55%) of the title compound (BAK-KA356).



BAK-KA348 BAK-KA356

^{1}H-NMR($CDCl_3$)δ:

2.79 (t, J=7.2Hz, 2H), 3.49 (t, J=7.2Hz, 2H), 3.70 (s, 3H), 3.86 (s, 3H), 3.87 (s, 3H), 4.02 (s, 2H), 6.60-6.79 (m, 3H), 7.53 (s, 2H), 9.00 (s, 1H)

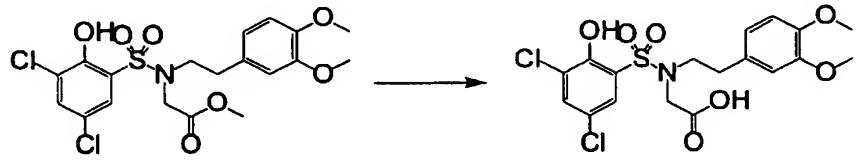
MS(EI)E/Z477(M),479(M+2)

Preparation Example 127

Synthesis of

[[(3,5-dichloro-2-hydroxyphenyl)sulfonyl][2-(3,4-dimethoxyphenyl)ethyl]amino]acetic acid

The title compound (BAK-KA357) was obtained at a yield of 87% in the same manner as in Preparation Example 116.



BAK-KA356. BAK-KA357

^{1}H-NMR($CDCl_3$)δ:

2.79 (t, J=7.2Hz, 2H), 3.51 (t, J=7.2Hz, 2H), 3.85 (s, 3H), 3.86 (s, 3H), 4.09 (s, 2H), 6.48-6.75 (m, 3H), 7.51 (d, J=2.5Hz, 1H), 7.53 (d, J=2.5Hz, 1H)

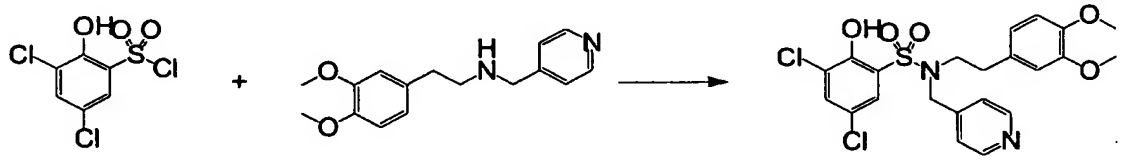
MS(EI)E/Z463(M),465(M+2)

Preparation Example 128

Synthesis of

3,5-dichloro-N-[2-(3,4-dihydroxyphenyl)ethyl]-2-hydroxy-N-[(4-pyridinyl)methyl] benzenesulfonamide

A mixture of 1.00 g (5.79 mmol) of 3,5-benzenesulfonyl chloride, 1.50 g (5.50 mmol) of BAK-KA353-2 obtained in Preparation Example 124, 2.42 ml (17.3 mmol) of triethylamine, and 60 ml of chloroform was stirred for 4.5 hours at room temperature. Saturated aqueous solution of sodium hydrogencarbonate was added to the reaction solution and the mixture was extracted with chloroform. The resulting organic layer was washed with saturated brine and dried over anhydrous sodium sulfate. After concentration, the crude product was purified by silica gel column chromatography (chloroform : methanol = 50 : 1) and recrystallized from methylene chloride-hexane to obtain 821 mg (yield: 29%) of the title compound (BAK-KA358).



BAK-KA353-2 BAK-KA358

^{1}H-NMR($CDCl_3$)δ:

2.64 (t, J=7.2Hz, 2H), 3.44 (t, J=7.2Hz, 2H), 3.81 (s, 3H), 3.85 (s, 3H), 4.42 (s, 2H), 6.48-6.75 (m, 3H), 7.19 (d, J=6.0Hz, 2H), 7.47 (d, J=2.5Hz, 1H), 7.55 (d, J=2.5Hz, 1H), 8.60 (d, J=6.0Hz, 2H)

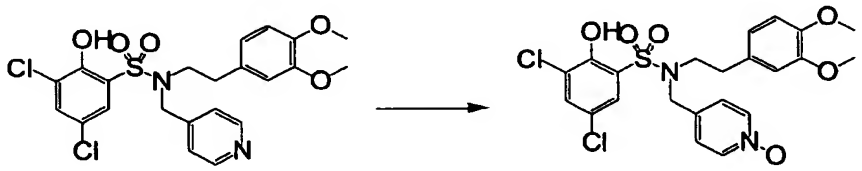
MS(EI)E/Z496(M),498(M+2)

Preparation Example 129

Synthesis of

4-[[[(3,5-dichloro-2-hydroxyphenyl)sulfonyl][2-(3,4-dimethoxyphenyl)ethyl]amino] methyl]pyridin-1-oxide

A mixture of 300 mg (0.60 mmol) of BAK-KA358 obtained in Preparation Example 128, 156 mg (0.90 mmol) of m-CPBA, and 12 ml of methylene chloride was stirred for four hours at room temperature. Diethyl ether was added to the reaction solution and the precipitated crystals were collected by filtration and washed with diethyl ether to obtain 257 mg (yield: 83%) of the title compound (BAK-KA360).



BAK-KA358 BAK-KA360

^{1}H-NMR($CDCl_3$)δ:

2.63 (t, J=7.2Hz, 2H), 3.44 (t, J=7.2Hz, 2H), 3.83 (s, 3H), 3.85 (s, 3H), 4.34 (s, 2H), 6.45-6.73 (m, 3H), 7.18 (d, J=7.0Hz, 2H), 7.54 (d, J=2.5Hz, 1H), 7.57 (d, J=2.5Hz, 1H), 8.19 (d, J=7.0Hz, 2H)

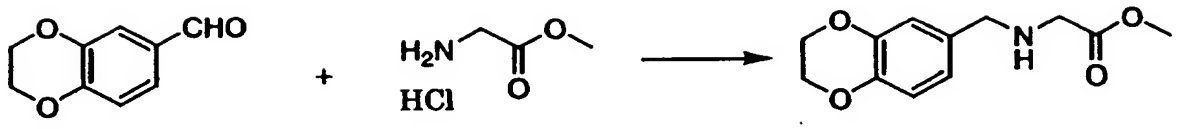
MS(FAB) +FAB513.1(M+1)

-FAB511.0(M-1)

Preparation Example 130

Synthesis of methyl [[(2,3-dihydro-1,4-benzodioxin-6-yl)methyl]amino]acetate

A mixture of 2.00 g (12.2 mmol) of 3,4-ethylenedioxybenzaldehyde, 1.53 g (12.2 mmol) of glycine methyl ester hydrochloride, 613 mg (9.75 mmol) of sodium cyanotrihydroboride, and 200 ml of anhydrous methanol was stirred for 23 hours at room temperature. After concentrating the reaction solution, saturated aqueous solution of sodium hydrogencarbonate was added to the reaction product and the mixture was extracted with diethyl ether. The resulting organic layer was dried over anhydrous sodium sulfate. After concentration, the resulting crude product was purified by silica gel column chromatography (hexane : ethyl acetate = 1 : 1 → chloroform : methanol = 20 : 1) to obtain 804 mg (yield: 28%) of the title compound (BAK-KA375).



BAK-KA375

^{1}H-NMR($CDCl_3$)δ:

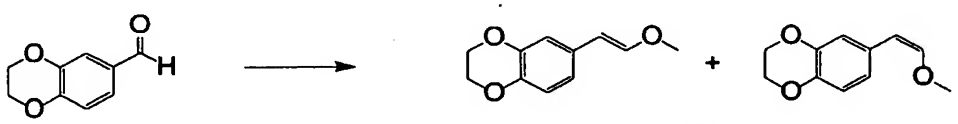
3.40 (s, 2H), 3.69 (s, 2H), 3.72 (s, 3H), 4.24 (s, 4H), 6.79-6.84 (m, 3H)

MS(EI)E/Z237(M)

Preparation Example 131

Synthesis of 2,3-dihydro-6-[(E)-2-methoxyvinyl]-1,3-benzodioxine and 2,3-dihydro-6-[(Z)-2-methoxyvinyl]-1,3-benzodioxine

1.06 g (26.5 mmol) of sodium hydride (60% in oil) was added to 54 ml of anhydrous methanol at 0°C under nitrogen atmosphere. 8.27 g (24.1 mmol) of methylenedioxy triphenylphosphine chloride in 50 ml of anhydrous methanol was added dropwise to the mixture, followed by stirring for 30 minutes at room temperature. After concentration, methanol in the reaction solution was removed by azeotropic distillation using benzene and the resulting reaction product was dried under reduced pressure. 3.0 g (18.3 mmol) of 3,4-ethylenedioxybenzaldehyde in 64 ml of benzene was added to the residue and the mixture was heated to reflux for three hours and stirred for 19 hours at room temperature. After concentration of the reaction solution, the crude product was purified by silica gel column chromatography (hexane : ethyl acetate = 10 : 1) to obtain 3.81 g (quantitative yield) of the title compound (BAK-KA377).



BAK-KA377

^{1}H-NMR($CDCl_3$)δ:

3.65, 3.74 (s, 3H×2), 4.23, 4.24 (s, 4H×2), 5.11 (d, J=7.0Hz, 1H),

5.70 (d, J=12.9Hz, 1H), 6.04 (d, J=7.0Hz, 1H), 6.71-6.79 (m, 4H),

6.90 (d, J=12.9Hz, 1H), 6.98-7.21 (m, 2H)

MS(EI)E/Z384(M)

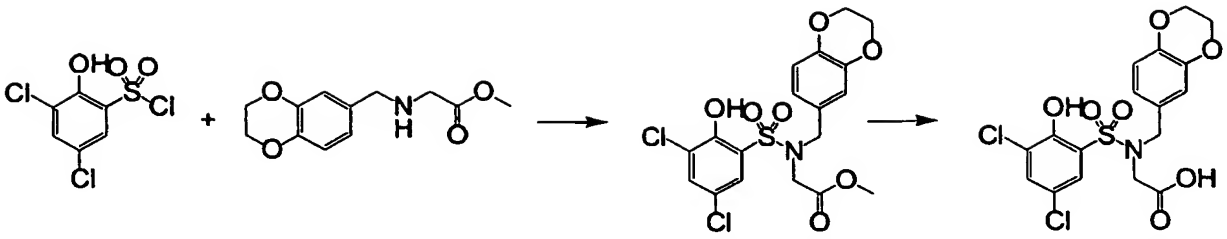
Preparation Example 132

Synthesis of

[[(3,5-dichloro-2-hydroxyphenyl)sulfonyl][(2,3-dihydro-1,4-benzodioxin-6-yl)methyl] amino]acetic acid

A mixture of 585 mg (3.39 mmol) of 3,5-benzenesulfonyl chloride, 804 mg (3.39 mmol) of BAK-KA375 obtained in Preparation Example 130, 1.42 ml (10.2 mmol) of triethylamine, and 35 ml of chloroform was stirred for 3.5 hours at room temperature. Saturated aqueous solution of sodium hydrogencarbonate was added to the reaction solution and the mixture was extracted with chloroform. The resulting organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate. After concentration, the resulting crude product was purified by silica gel column chromatography (hexane : ethyl acetate = 2 : 1 → 1 : 1) to obtain 971 mg (yield: 62%) of a methyl ester compound (BAK-KA379) of the title compound.

A mixture of 971 mg (2.10 mmol) of BAK-KA379 obtained above, 252 mg (6.30 mmol) of sodium hydroxide, 5 ml of methanol, and 5 ml of water was stirred for 4.5 hours at room temperature. 1 mol/l of hydrochloric acid was added to the reaction solution, the mixture was extracted with chloroform, and the resulting organic layer was dried over anhydrous magnesium sulfate. After concentration, the resulting crude product was recrystallized from methylene chloride-hexane to obtain 762 mg (yield: 81%) of the title compound (BAK-KA380).



BAK-KA375 BAK-KA379 BAK-KA380

^{1}H-NMR($CDCl_3$)δ:

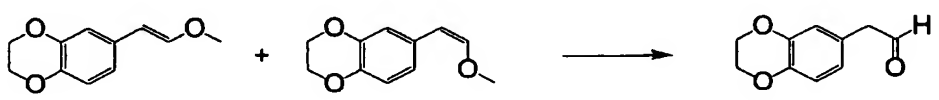
4.05 (s, 2H), 4.25 (s, 4H), 4.35 (s, 2H), 6.68 (dd, J=2.1, 8.2Hz, 1H), 6.74 (d, J=2.1Hz, 1H), 6.82 (d, J=8.2Hz, 1H), 7.56 (d, J=2.5Hz, 1H), 7.60 (d, J=2.5Hz, 1H)

MS(EI)E/Z446(M)

Preparation Example 133

Synthesis of (2,3-dihydro-1,4-benzoxy-6-yl)acetaldehyde

A mixture of 3.81 g (19.8 mmol) of BAK-KA377 obtained in Preparation Example 131, 1.82 ml of sulfuric acid, 95 ml of anhydrous tetrahydrofuran, and 18 ml of water was heated to reflux for five hours. After concentrating the reaction solution, water was added to the residue and the mixture was extracted with diethyl ether. The resulting organic layer was washed with saturated brine and dried over anhydrous sodium sulfate. After concentration, the resulting crude product was purified by silica gel column chromatography (hexane : ethyl acetate = 5 : 1) to obtain 2.67 g (yield: 76%)of the title compound (BAK-KA381).



BAK-KA377 BAK-KA381

^{1}H-NMR($CDCl_3$)δ:

3.57 (d, J=2.4Hz, 1H), 4.26 (s, 4H), 6.64-6.88 (m, 3H), 9.70 (d, J=2.4Hz, 1H)

MS(EI)E/Z178(M)

Preparation Example 134

Synthesis of methyl [[2-(2,3-dihydro-1,4-benzodioxin-6-yl)ethyl]amino]acetate

A mixture of 2.67 g (15.0 mmol) of BAK-KA381 obtained in Preparation Example 133, 2.50 g (19.9 mmol) of glycine methyl ester hydrochloride, 754 mg (12.0 mmol) of sodium cyanotrihydroboride, and 200 ml of anhydrous methanol was stirred for 14.5 hours at room temperature. Saturated aqueous solution of sodium hydrogencarbonate was added to the reaction solution and the mixture was extracted with diethyl ether. The resulting organic layer was washed with saturated brine and dried over anhydrous sodium sulfate. After concentration, the resulting crude product was purified by silica gel column chromatography (hexane : ethyl acetate = 1 : 1 → chloroform : methanol = 10 : 1) to obtain 2.25 g (yield: 60%)of the title compound (BAK-KA383).

BAK-KA381 BAK-KA383

^{1}H-NMR($CDCl_3$)δ:

2.66-2.74 (m, 2H), 2.80-2.88 (m, 2H), 3.42 (s, 2H), 3.72 (s, 2H), 4.24 (s, 4H), 6.65-6.81 (m, 3H)

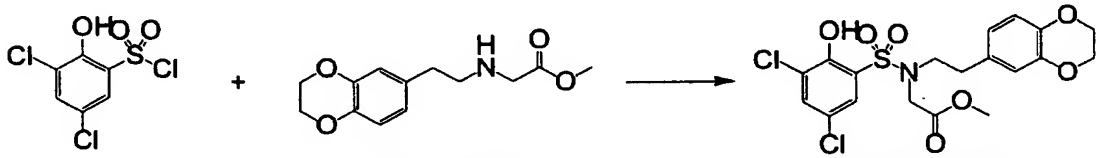
MS(EI)E/Z251(M)

Preparation Example 135

Synthesis of methyl [[(3,5-dichloro-2-hydroxyphenyl)sulfonyl][2-(2,3-dihydro-1,4-benzodioxin-6-yl) ethyl]amino]acetate

A mixture of 1.54 g (8.95 mmol) of 3,5-benzenesulfonyl chloride, 2.25 g (8.95 mmol) of BAK-KA383 obtained in Preparation Example 134, 3.75 ml (26.9 mmol) of triethylamine, and 89 ml of chloroform was stirred for 16 hours at room temperature. 1

mol/l of hydrochloric acid was added to the reaction solution and the mixture was extracted with chloroform. The resulting organic layer was washed with saturated aqueous solution of sodium hydrogencarbonate and saturated brine and dried over anhydrous sodium sulfate. After concentration, the resulting crude product was purified by silica gel column chromatography (hexane : ethyl acetate = 2 : 1) to obtain 2.21 g (yield: 52%) of the title compound (BAK-KA384).



BAK-KA383 BAK-KA384

^{1}H-NMR($CDCl_3$)δ:

2.74 (t, J=7.2Hz, 2H), 3.45 (t, J=7.2Hz, 2H), 3.69 (s, 3H), 4.04 (s, 2H), 4.24 (s, 4H), 6.54-6.78 (m, 3H), 7.54 (s, 2H)

MS(EI)E/Z475(M)

Preparation Example 136

Synthesis of

[[(3,5-dichloro-2-hydroxyphenyl)sulfonyl][2-(2,3-dihydro-1,4-benzodioxin-6-yl)ethyl] amino]acetic acid

The title compound (BAK-KA385) was obtained at a yield of 90% in the same manner as in Preparation Example 116.

BAK-KA384 BAK-KA385

^{1}H-NMR($CDCl_3$)δ:

2.74 (t, J=7.1Hz, 2H), 3.47 (t, J=7.1Hz, 2H), 4.02 (s, 2H), 4.24 (s, 4H),

6.54-6.78 (m, 3H), 7.52 (d, J=2.5Hz, 1H), 7.55 (d, J=2.5Hz, 1H)

MS(EI)E/Z461(M)

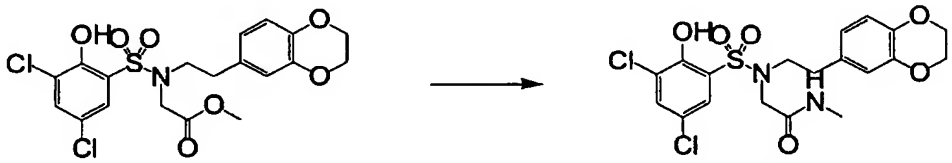
Preparation Example 137

Synthesis of

2-[[(3,5-dichloro-2-hydroxyphenyl)sulfonyl](3,4-dimethoxyphenethyl)amino]-N-methylacetamide

2.76 g (5.77 mmol) of BAK-KA384 obtained in Preparation Example 135, 5.00 ml of methylamine methanol solution (40% solution), 5.00 ml of methanol was stirred for 17 hours at room temperature. 1 mol/l of hydrochloric acid was added to the reaction solution and the mixture was extracted with chloroform. The resulting organic layer was dried over anhydrous magnesium sulfate. After concentration, the resulting reaction product was recrystallized from methylene chloride-hexane to obtain 1.95 g of the title compound (BAK-KA389).

The filtrate after removing crystals was concentrated and purified by silica gel column chromatography (chloroform : methanol = 30 : 1) to obtain 358 mg (yield: 84%) of the same title compound (BAK-KA 389).



BAK-KA384 BAK-KA389

^{1}H-NMR($CDCl_3$)δ:

1.59 (t, J=7.6Hz, 2H), 2.80 (d, J=4.9Hz, 3H), 3.48 (t, J=7.6Hz, 2H),

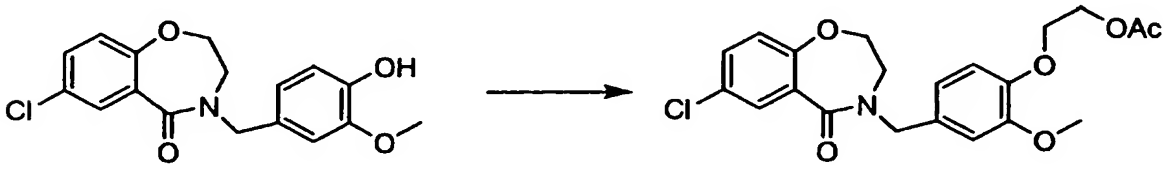
3.86 (s, 8H), 6.62 (brs, 1H), 6.63-6.80 (m, 3H), 7.56 (s, 2H), 9.17 (s, 1H)

MS(EI)E/Z476(M^+)

Preparation Example 138

Synthesis of 2-[4-[[7-chloro-5-oxo-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]methyl]-2-methoxyphenoxy]ethyl acetate

0.13 ml (1.21 mmol) of 2-bromoethyl acetate was added to a mixture of 201.6 mg (0.604 mmol) of BAK-G473 obtained in Preparation Example 75, 167 mg (1.21 mmol) of potassium carbonate, and 4 ml of DMF. The mixture was stirred for 24 hours at room temperature. Water was added to the reaction solution, the mixture was extracted with ethyl acetate, and the resulting organic layer was dried over anhydrous sodium sulfate. After concentration, the resulting crude product was purified by silica gel column chromatography (hexane : ethyl acetate = 4 : 3) to obtain 219 mg (yield: 86%) of the title compound (BAK-G687).



^{1}H-NMR($CDCl_3$)δ:

2.10 (s, 3H), 3.45 (t, J=5.3Hz, 2H), 3.86 (s, 3H), 4.13 (t, J=5.3Hz, 2H), 4.23 (m, 2H), 4.44 (m, 2H), 4.75 (s, 2H), 6.80-7.00 (m, 4H), 7.36 (dd, J=2.6, 8.7Hz, 1H), 7.85 (d, J=2.6Hz, 1Hz)

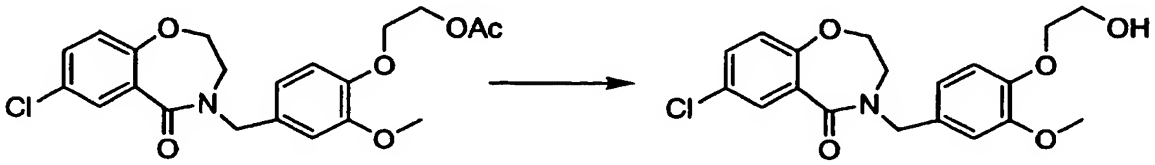
Preparation Example 139

Synthesis of

7-chloro-4-[4-(2-hydroxyethoxy)-3-methoxybenzyl]-3,4-dihydro-1,4-benzoxazepin-5(2H)-one

2 ml of 10% aqueous solution of sodium hydroxide was added to a mixture of 200 mg (0.476 mmol) of BAK-G687 obtained in Preparation Example 138 and 4 ml of methanol. The mixture was stirred for two hours at room temperature. Diluted

hydrochloric acid was added to the reaction solution, the mixture was extracted with ethyl acetate, and the resulting organic layer was dried over anhydrous sodium sulfate. After concentration, the resulting crude product was purified by silica gel column chromatography (hexane : ethyl acetate = 1 : 2) to obtain 165 mg (yield: 92%) of the title compound (BAK-G692).



BAK-G687 BAK-G692

^{1}H-NMR($CDCl_3$)δ:

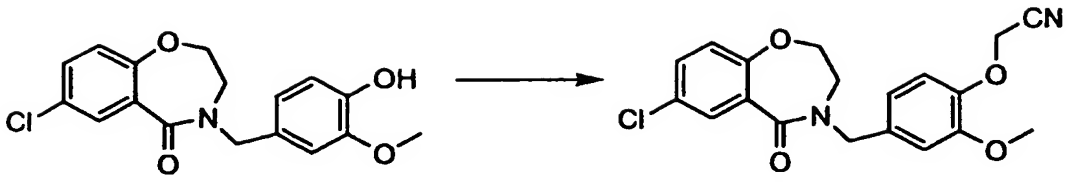
2.89 (brs, 1H), 3.45 (t, J=5.3Hz, 2H), 3.85 (s, 3H), 3.94 (brs, 2H),
4.05-4.20 (m, 4H), 4.75 (s, 2H), 6.80-7.00 (m, 4H),
7.36 (dd, J=2.7, 8.7Hz, 1H), 7.84 (d, J=2.7Hz, 1H)

MS(EI)E/Z377(M+)

Preparation Example 140

Synthesis of [4-[[7-chloro-5-oxo-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]methyl]-2-methoxyphenoxy]acetonitrile

0.085 ml (1.21 mmol) of bromoacetonitrile was added to a mixture of 202.3 mg (0.606 mmol) of BAK-G473 obtained in Preparation Example 75, 167 mg (1.21 mmol) of potassium carbonate, and 4 ml of DMF. The mixture was stirred for two hours at room temperature. Water was added to the reaction solution, the mixture was extracted with ethyl acetate, and the resulting organic layer was dried over anhydrous sodium sulfate. After concentration, the resulting crude product was purified by silica gel column chromatography (hexane : ethyl acetate = 1 : 1) to obtain 224 mg (yield: 99%) of the title compound (BAK-G689).



BAK-G473 BAK-G689

^{1}H-NMR($CDCl_3$)δ:

3.47 (t, J=5.0Hz, 2H), 3.88 (s, 3H), 4.17 (t, J=5.0Hz, 2H), 4.77 (s, 2H), 4.83 (s, 2H), 6.88 (dd, J=2.0, 8.1Hz, 1H), 6.95 (d, J=8.6Hz, 1H), 7.00 (d, J=2.0Hz, 1H), 7.03 (d, J=8.1Hz, 1H), 7.37 (dd, J=2.7, 8.6Hz, 1H), 7.85 (d, J=2.7Hz, 1H)

MS(EI)E/Z372(M^+)

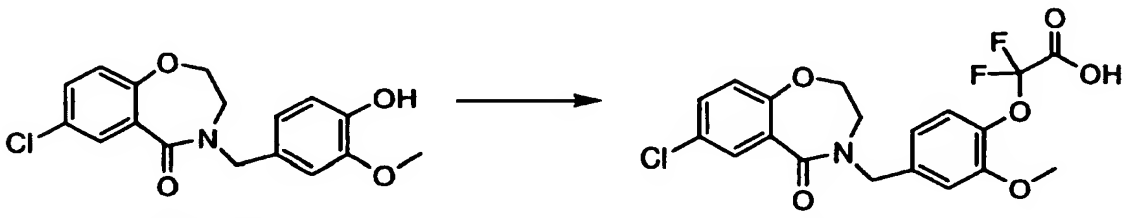
Preparation Example 141

Synthesis of [4-[[7-chloro-5-oxo-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]methyl]-2-methoxyphenoxy]difluoroacetic acid

0.39 ml (3.00 mmol) of ethyl bromodifluoroacetate was added to a mixture of 200 mg (0.599 mmol) of BAK-G473 obtained in Preparation Example 75, 414 mg (3.00 mmol) of potassium carbonate, and 4 ml of DMF. The mixture was stirred for 24 hours at 50°C. Water was added to the reaction solution, the mixture was extracted with ethyl acetate, and the resulting organic layer was dried over anhydrous sodium sulfate. After concentration, the resulting crude product was purified by silica gel column chromatography (hexane : ethyl acetate = 2 : 1) to obtain 197.7 mg (yield: 72%) of an ethyl ester compound.

2 ml of 10% aqueous solution of sodium hydroxide was added to a mixture of 180 mg (0.395 mmol) of the ethyl ester compound obtained above and 4 ml of methanol. The mixture was stirred for three hours at room temperature. Diluted hydrochloric acid was added to the reaction solution, the mixture was extracted with ethyl acetate, and the

resulting organic layer was dried over anhydrous sodium sulfate. After concentration, 188 mg of the title compound (BAK-G693) was obtained as a crude product.



BAK-G473 BAK-G693

^{1}H-NMR($CDCl_3$)δ:

3.49 (t, J=5.2Hz, 2H), 3.81 (s, 3H), 4.19 (t, J=5.2Hz, 2H), 4.79 (s, 2H), 6.85 (dd, J=1.9, 8.1Hz, 1H), 6.96 (d, J=8.7Hz, 1H), 6.99 (d, J=1.9Hz, 1H), 7.21 (d, J=8.1Hz, 1H), 7.39 (dd, J=2.6, 8.7Hz, 1H), 7.83 (d, J=2.6Hz, 1H)

MS(EI)E/Z427(M^+)

Preparation Example 142

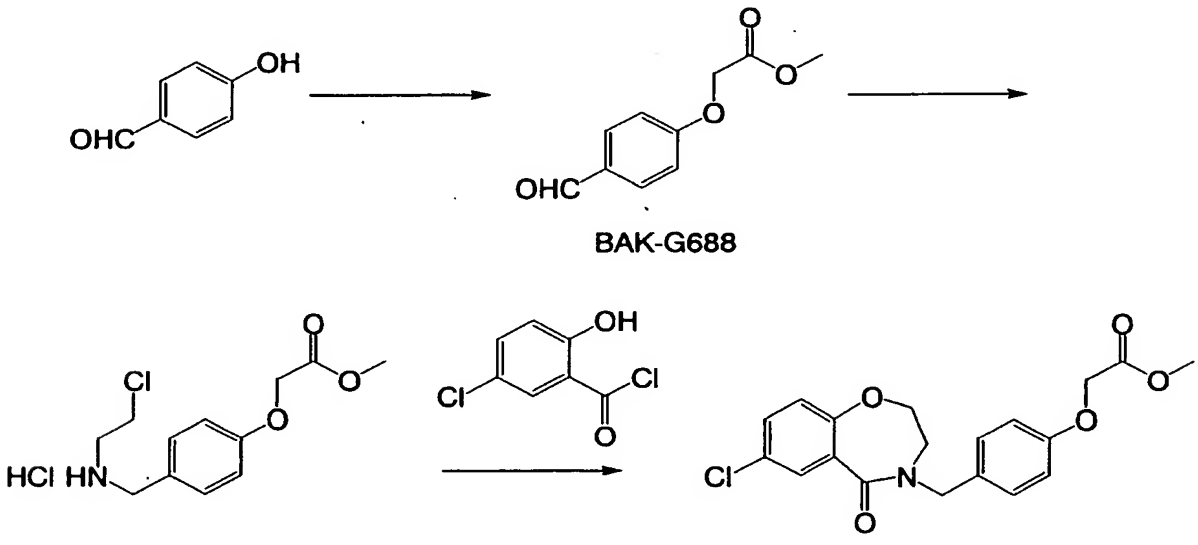
Synthesis of methyl [4-[[7-chloro-5-oxo-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]methyl]phenoxy] acetate

9.3 ml (98.36 mmol) of methyl bromoacetate was added to a mixture of 10.00 g (81.97 mmol) of 4-hydroxybenzaldehyde, 22.62 g (163.9 mmol) of potassium carbonate, and 100 ml of acetone. The mixture was stirred for 24 hours at room temperature. The reaction solution was filtrated and the filtrate was concentrated. Water was added to the residue, the mixture was extracted with ethyl acetate, and the resulting organic layer was dried over anhydrous sodium sulfate. After concentration, the resulting crude product was purified by silica gel column chromatography (hexane : ethyl acetate = 2 : 1) to obtain 14.74 g (yield: 93%) of methyl(4-formylphenoxy)acetate (BAK-G688).

A mixture of 2.04 g (10.5 mmol) of the obtained BAK-G688, 20 ml of ethanol, 2.44 g (21 mmol) of 2-chloroethylamine hydrochloride, and 0.6 ml of acetic acid was stirred for 30 minutes at room temperature. The reaction solution was cooled with ice,

279 mg (7.35 mmol) of sodium borohydride was added to the solution, and the mixture was stirred for one hour at room temperature. The precipitated crystals were collected by filtration and dried under reduced pressure to obtain 1.75 g (yield: 57%) of (2-chloroethyl)[4-[(methoxycarbonyl)methoxy]benzyl]ammonium chloride (BAK-G699).

A mixture of 1.23 g (4.18 mmol) of the obtained BAK-G699, 12 ml of ethyl acetate, and 3.1 ml (20.9 mmol) of DBU was cooled with ice. 1.6 g (8.36 mmol) of 5-chlorosalicylic acid in 16 ml of ethyl acetate was added dropwise to the mixture. The reaction solution was stirred for four hours at room temperature. Diluted hydrochloric acid was added to the reaction solution, the mixture was extracted with ethyl acetate, and the resulting organic layer was dried over anhydrous sodium sulfate. After concentration, the resulting crude product was purified by silica gel column chromatography (hexane : ethyl acetate = 2 : 1) to obtain 702.7 mg (yield: 45%) of the title compound (BAK-G701).



^{1}H-NMR($CDCl_3$)δ:

3.43 (t, J=5.1Hz, 2H), 3.81 (s, 3H), 4.15 (t, J=5.1Hz, 2H), 4.64 (s, 2H), 4.75 (s, 2H), 6.89 (d, J=8.7Hz, 2H), 6.93 (d, J=8.6Hz, 1H),

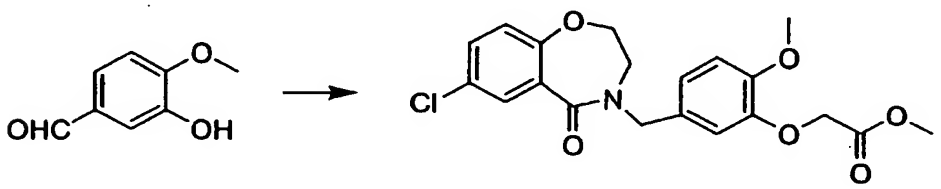
7.28 (d, J=8.7Hz, 2H), 7.35 (dd, J=2.7, 8.6Hz, 1H), 7.85 (d, J=2.7Hz, 1H)

MS(EI)E/Z375(M^+)

Preparation Example 143

Synthesis of methyl [5-[[7-chloro-5-oxo-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]methyl]-2-methoxyphenoxy]acetate

The title compound (BAK-G702) was obtained in the same manner as in the Preparation Example 142.



BAK-G702

^{1}H-NMR($CDCl_3$)δ:

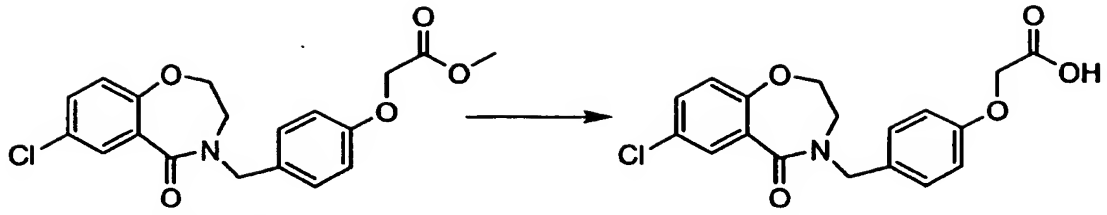
3.42 (t, J=5.0Hz, 2H), 3.76 (s, 3H), 3.88 (s, 3H), 4.12 (t, J=5.0Hz, 2H), 4.70 (s, 2H), 4.72 (s, 2H), 6.80-6.93 (m, 3H), 6.93 (d, J=8.7Hz, 1H), 7.36 (dd, J=2.7, 8.7Hz, 1H), 7.84 (d, J=2.7Hz, 1H)

MS(EI)E/Z405(M^+)

Preparation Example 144

Synthesis of [4-[[7-chloro-5-oxo-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]methyl]phenoxy]acetic acid

The title compound (BAK-G703) was obtained in the same manner as in the Preparation Example 68.



BAK-G701 BAK-G703

^{1}H-NMR($CDCl_3$)δ:

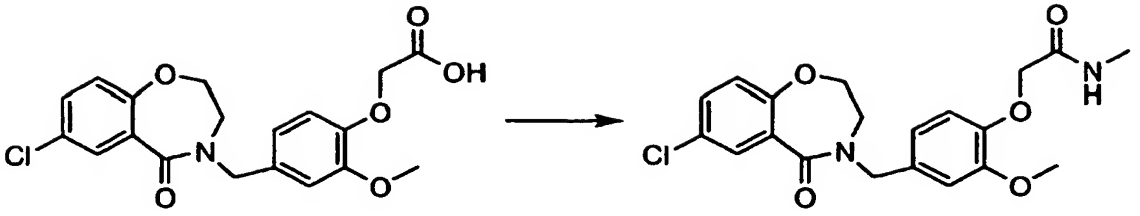
3.44 (t, J=5.0Hz, 2H), 4.15 (t, J=5.0Hz, 2H), 4.66 (s, 2H), 4.76 (s, 2H), 6.90 (d, J=8.7Hz, 2H), 6.93 (d, J=8.7Hz, 1H), 7.28 (d, J=8.7Hz, 2H), 7.36 (dd, J=2.7, 8.7Hz, 1H), 7.85 (d, J=2.7Hz, 1H)

MS(EI)E/Z361(M^+)

Preparation Example 145

Synthesis of 2-[4-[[7-chloro-5-oxo-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]methyl]-2-methoxyphenoxy]-N-methylacetamide

A mixture of 1.01 g (2.58 mmol) of BAK-G475 obtained in Preparation Example 77, 1.35 ml (7.74 mmol) of DIEA, 627 mg (3.87 mmol) of 1,1'-carbonyldiimidazole, and 20 ml of DMF was stirred for 30 minutes at room temperature. 351 mg (5.16 mmol) of methylamine hydrochloride was added to the reaction solution and the mixture was stirred for three hours at room temperature. Diluted hydrochloric acid was added to the reaction solution, the mixture was extracted with ethyl acetate, and the resulting organic layer was dried over anhydrous sodium sulfate. After concentration, the resulting crude product was purified by silica gel column chromatography (ethyl acetate) to obtain 893.9 mg (yield: 86%) of the title compound (BAK-G719).



BAK-G475 BAK-G719

^{1}H-NMR($CDCl_3$)δ:

2.91 (d, J=5.0Hz, 3H), 3.46 (t, J=5.0Hz, 2H), 3.88 (s, 3H),

4.16 (t, J=5.0Hz, 2H), 4.52 (s, 2H), 4.76 (s, 2H), 6.80-7.00 (m, 5H),

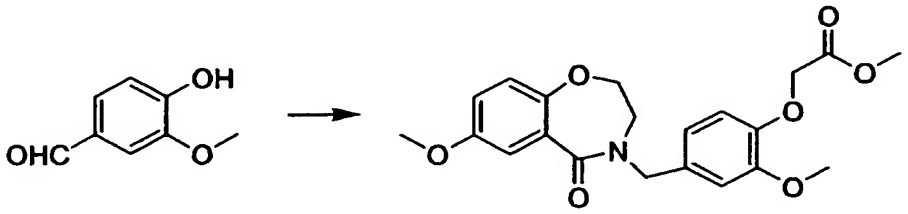
7.37 (dd, J=2.7, 8.6Hz, 1H), 7.85 (d, J=2.7Hz, 1H)

MS(EI)E/Z404(M^+)

Preparation Example 146

Synthesis of methyl [2-methoxy-4-[[7-methoxy-5-oxo-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl] methyl]phenoxy]acetate

The title compound (BAK-G706) was obtained in the same manner as in Preparation Example 142.



BAK-G706

^{1}H-NMR($CDCl_3$)δ:

3.42 (t, J=5.5Hz, 2H), 3.80 (s, 3H), 3.83 (s, 3H), 3.88 (s, 3H),

4.07 (t, J=5.5Hz, 2H), 4.70 (s, 2H), 4.77(s, 2H), 6.75-7.00(m, 5H),

7.31(dd, J=0.4, 2.5Hz, 1H)

MS(EI)E/Z401(M^+)

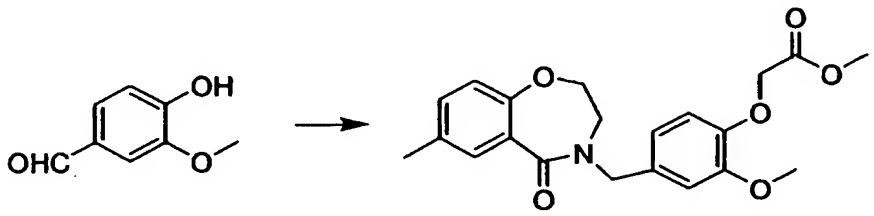
Preparation Example 147

Synthesis of methyl

[2-methoxy-4-[[7-methyl-5-oxo-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]methyl]-

phenoxy]acetate

The title compound (BAK-G708) was obtained in the same manner as in Preparation Example 142.



BAK-G708

^{1}H-NMR($CDCl_3$)δ:

2.35 (s, 3H), 3.42 (t, J=5.3Hz, 2H), 3.80 (s, 3H), 3.88 (s, 3H),

4.11 (t, J=5.3Hz, 2H), 4.69 (s, 2H), 4.76 (s, 2H), 6.77 (d, J=8.1Hz, 1H),

6.80 (dd, J=1.7, 8.1Hz, 1H), 6.89 (d, J=8.3Hz, 1H), 6.97 (d, J=1.7Hz, 1H),

7.22 (dd, J=2.1, 8.3Hz, 1H), 7.63 (d, J=2.1Hz, 1H)

MS(EI)E/Z385(M^+)

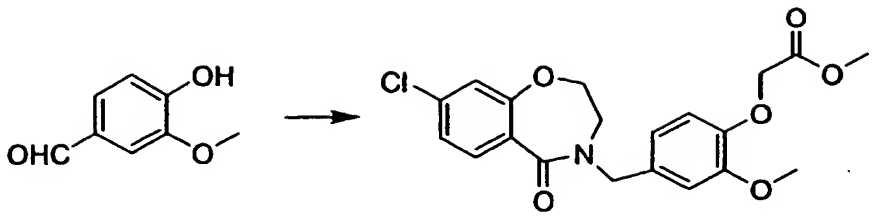
Preparation Example 148

Synthesis of methyl

[4-[[8-chloro-5-oxo-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]methyl]-2-

methoxyphenoxy]acetate

The title compound (BAK-G710) was obtained in the same manner as in Preparation Example 142.



BAK-G710

^{1}H-NMR($CDCl_3$)δ:

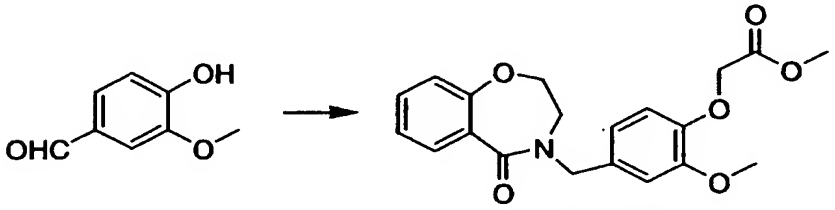
3.46 (t, J=5.2Hz, 2H), 3.80 (s, 3H), 3.87 (s, 3H), 4.18 (t, J=5.2Hz, 2H), 4.70 (s, 2H), 4.75 (s, 2H), 6.70-6.85 (m, 2H), 6.94 (d, J=1.6Hz, 1H), 7.01 (d, J=2.0Hz, 1H), 7.15 (dd, J=2.0, 8.4Hz, 1H), 7.84 (d, J=8.4Hz, 1H)

MS(EI)E/Z405(M^+)

Preparation Example 149

Synthesis of methyl [2-methoxy-4-[[5-oxo-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]methyl]phenoxy]acetate

The title compound (BAK-G716) was obtained in the same manner as in Preparation Example 142.



BAK-G716

^{1}H-NMR($CDCl_3$)δ:

3.45 (t, J=5.4Hz, 2H), 3.80 (s, 3H), 3.87 (s, 3H), 4.15 (t, J=5.4Hz, 2H), 4.70 (s, 2H), 4.77 (s, 2H), 6.78 (d, J=8.1Hz, 1H), 6.84 (dd, J=1.7, 8.1Hz, 1H), 6.97 (d, J=1.7Hz, 1H), 6.99 (dd, J=1.8, 7.7Hz, 1H), 7.19 (dt, 1.8, 7.7Hz, 1H), 7.43 (dt, J=1.8, 7.7Hz, 1H), 7.86 (dd, J=1.8, 7.7Hz, 1H)

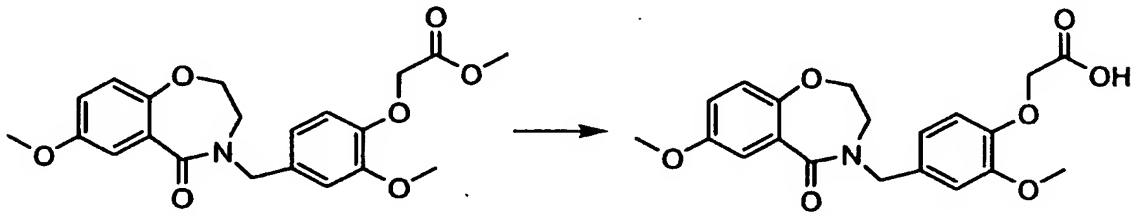
MS(EI)E/Z371(M^+)

Preparation Example 150

Synthesis of

[2-methoxy-4-[[7-methoxy-5-oxo-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]methyl] phenoxy]acetic acid

The title compound (BAK-G711) was obtained in the same manner as in Preparation Example 68.



BAK-G706 BAK-G711

^{1}H-NMR(DMSO-d_6)δ:

3.44 (t, J=5.2Hz, 2H), 3.76 (s, 6H), 4.11t, J=5.2Hz, 2H), 463 (s, 2H), 4.66 (s, 2H), 6.80-7.00 (m, 4H), 7.05 (dd, J=2.8, 8.8Hz, 1H), 7.14 (d, J=2.8Hz, 1H).

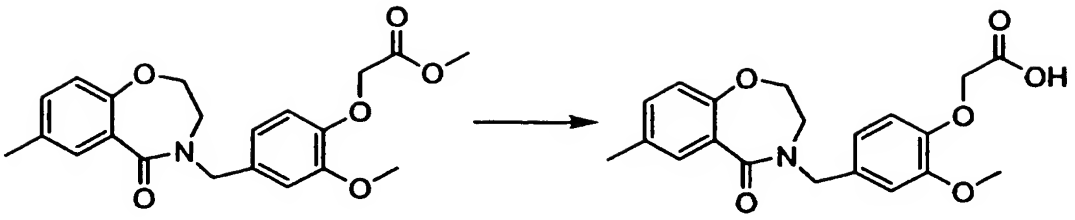
MS(EI)E/Z387(M^+)

Preparation Example 151

Synthesis of

[2-methoxy-4-[[7-methyl-5-oxo-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]methyl] phenoxy]acetic acid

The title compound (BAK-G712) was obtained in the same manner as in Preparation Example 68.



BAK-G708 BAK-G712

^{1}H-NMR(DMSO-d_6)δ:

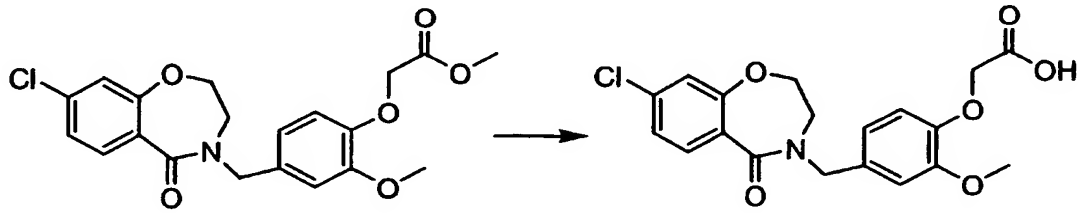
2.30 (s, 3H), 3.45 (t, J=5.1Hz, 1H), 3.76 (s, 3H), 4.15 (t, J=5.1Hz, 2H), 4.63 (s, 2H), 4.66 (s, 2H), 6.83 (brs, 2H), 6.92 (d, J=8.2Hz, 1H), 6.98 (brs, 1H), 7.27 (dd, J=2.1, 8.2Hz, 1H), 7.47 (d, J=2.1Hz, 1H)

MS(EI)E/Z371(M^+)

Preparation Example 152

Synthesis of [4-[[8-chloro-5-oxo-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]methyl]-2-methoxyphenoxy]acetic acid

The title compound (BAK-G713) was obtained in the same manner as in Preparation Example 68.



BAK-G710 BAK-G713

^{1}H-NMR(DMSO-d_6)δ:

3.52 (t, J=5.0Hz, 2H), 3.76 (s, 3H), 4.24 (t, J=5.0Hz, 2H), 4.63 (s, 2H), 4.66 (s, 2H), 6.83 (brs, 2H), 6.97 (brs, 1H), 7.13 (d, J=2.1Hz, 1H), 7.24 (dd, J=2.1, 8.4Hz, 1H), 7.74 (d, J=8.4Hz, 1H)

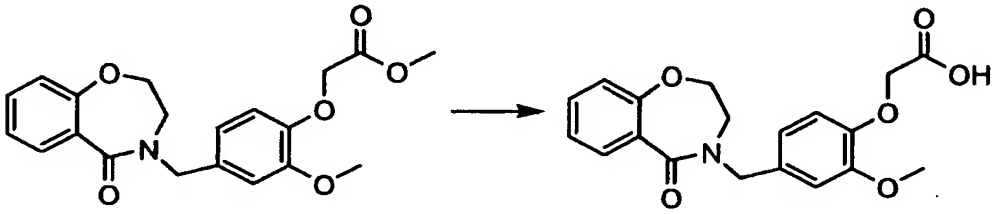
MS(EI)E/Z391(M^+)

Preparation Example 153

Synthesis of

[2-methoxy-4-[[5-oxo-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]methyl]phenoxy]acetic acid

The title compound (BAK-G717) was obtained in the same manner as in Preparation Example 68.



BAK-G716 BAK-G717

^{1}H-NMR(DMSO-d_6)δ:

3.48 (t, J=5.0Hz, 2H), 3.76 (s, 3H), 4.19 (t, J=5.0Hz, 2H), 4.63 (s, 2H), 4.67 (s, 2H), 6.83 (brs, 2H), 6.98 (brs, 1H), 7.03 (dd, J=1.8, 7.7Hz, 1H), 7.19 (dt, J=1.8, 7.7Hz, 1H), 7.47 (dt, J=1.8, 7.7Hz, 1H), 7.70 (dd, J=1.8, 7.7Hz, 1H)

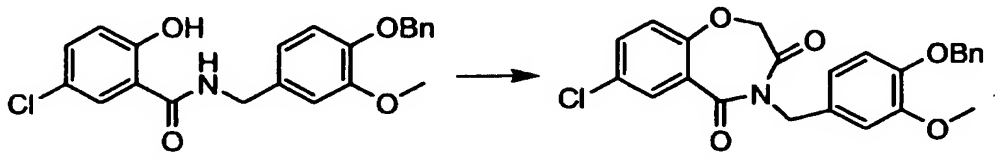
MS(EI)E/Z357(M^+)

Preparation Example 154

Synthesis of 4-[4-(benzyloxy)-3-methoxybenzyl]-7-chloro-1,4-benzoxazepine-3,5(2H, 4H)-dione

0.66 ml (8.16 mmol) of chloroacethyl chloride was added dropwise to a mixture of 810.9 mg (2.04 mmol) of BAK-G395 obtained in Preparation Example 43, 1.13 g (8.16 mmol) of potassium carbonate, and 16 ml of DMF while cooling with ice. The mixture was stirred for two hours at room temperature and further stirred for 20 hours at 40°C. Water was added to the reaction solution, the mixture was extracted with ethyl acetate, and the resulting organic layer was dried over anhydrous sodium sulfate. After

concentration, the resulting crude product was purified by silica gel column chromatography (hexane : ethyl acetate = 4 : 1) to obtain 754.3 mg (yield: 84%) of the title compound (BAK-G695).



BAK-G395 BAK-G695

^{1}H-NMR($CDCl_3$)δ:

3.88 (s, 3H), 4.76 (s, 2H), 5.11 (s, 2H), 5.12 (s, 2H), 6.79 (d, J=8.3Hz, 1H), 6.85-7.10 (m, 3H), 7.25-7.50 (m, 6H), 8.13 (d, J=2.6Hz, 1H)

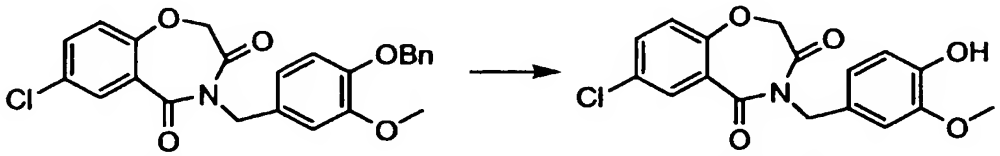
MS(EI)E/Z437(M^+)

Preparation Example 155

Synthesis of

7-chloro-4-(4-hydroxy-3-methoxybenzyl)-1,4-benzoxazepin-3,5(2H,4H)-dione

74 mg of 10% Pd-C was added to a mixture of 746.3 mg (1.70 mmol) of BAK-G695 obtained in Preparation Example 154 and 15 ml of ethyl acetate. The mixture was stirred under hydrogen atmosphere for two hours at room temperature. After filtrating the reaction solution through celite, the filtrate was concentrated to obtain 658.3 mg of the title compound (BAK-G696) as a crude product.



BAK-G695 BAK-G696

^{1}H-NMR($CDCl_3$)δ:

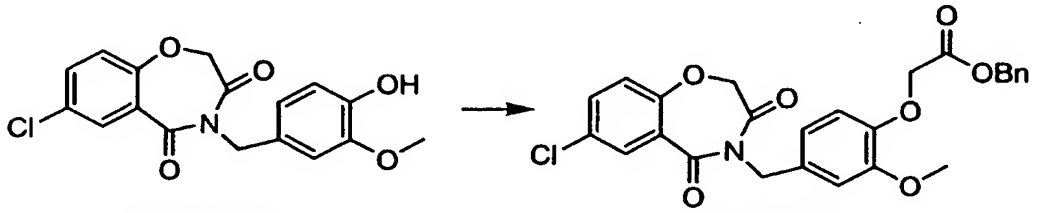
3.88 (s, 3H), 4.76 (s, 2H), 5.11 (s, 2H), 5.58 (s, 1H), 6.80-7.10 (m, 4H), 7.44 (dd, J=2.6, 8.7Hz, 1H), 8.13 (d, J=2.6Hz, 1H)

MS(EI)E/Z347(M^+)

Preparation Example 156

Synthesis of benzyl [4-[[7-chloro-3,5-dioxo-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]methyl]-2-methoxyphenoxy]acetate

0.58 ml (3.68 mmol) of benzyl bromoacetate was added to a mixture of 640 mg (1.84 mmol) of BAK-G696 obtained in Preparation Example 155, 508 mg (3.68 mmol) of potassium carbonate, and 10 ml of DMF. The mixture was stirred for three hours at room temperature. Water was added to the reaction solution, the mixture was extracted with ethyl acetate, and the resulting organic layer was dried over anhydrous sodium sulfate. After concentration, the resulting crude product was purified by silica gel column chromatography (hexane : ethyl acetate = 2 : 1) to obtain 737 mg (yield: 81%) of the title compound (BAK-G722).



^{1}H-NMR($CDCl_3$)δ:

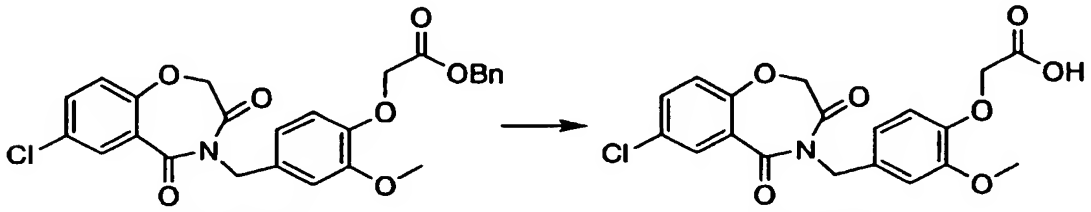
3.85 (s, 3H), 4.70 (s, 2H), 4.77 (s, 2H), 5.12 (s, 2H), 5.21 (s, 2H),
6.71 (d, J=8.2Hz, 1H), 6.93 (dd, J=8.2, 2.0Hz, 1H), 7.04 (d, J=2.0Hz, 1H),
7.05 (d, J=8.7Hz, 1H), 7.25-7.40 (m, 5H), 7.45 (dd, J=2.7, 8.7Hz, 1H),
8.13 (d, J=2.6Hz, 1H)

MS(EI)E/Z495(M^+)

Preparation Example 157

Synthesis of [4-[[7-chloro-3,5-dioxo-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]methyl]-2-methoxyphenoxy]acetic acid

70 mg of 10% Pd-C was added to a mixture of 720 mg (1.45 mmol) of BAK-G722 obtained in Preparation Example 155 and 10 ml of ethyl acetate. The mixture was stirred under hydrogen atmosphere for two hours at room temperature. After filtrating the reaction solution through celite, the filtrate was concentrated and the residue was recrystallized from ethanol to obtain 304.8 mg (yield: 52%) of the title compound (BAK-G723).



BAK-G722 BAK-G723

^{1}H-NMR(DMSO-d_6)δ:

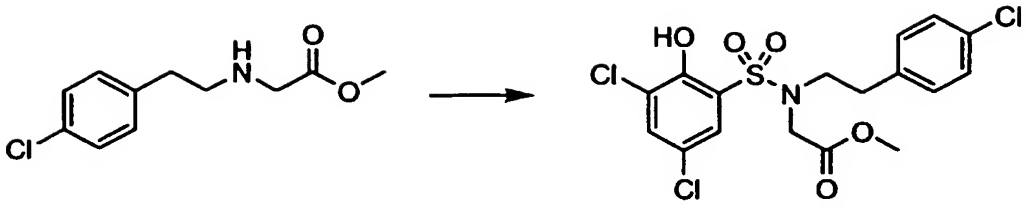
3.73 (s, 2H), 4.60 (s, 2H), 5.00 (s, 4H), 6.75 (brs, 2H), 6.93 (brs, 1H), 7.25 (d, J=8.7Hz, 1H), 7.68 (dd, J=2.7, 8.7Hz, 1H), 8.01 (d, J=2.7Hz, 1H), 13.00 (brs, 1H)

MS(EI)E/Z405(M^+)

Preparation Example 158

Synthesis of methyl [[2-(4-chlorophenyl)ethyl][(3,5-dichloro-2-hydroxyphenyl)sulfonyl]amino]acetate

The title compound (BAK-KA424) was obtained in the same manner as in Preparation Example 114.



BAK-KA424

^{1}H-NMR($CDCl_3$)δ:

2.83 (t, J=7.1Hz, 2H), 3.49 (t, J=7.1Hz, 2H), 3.70 (s, 3H), 4.34 (s, 2H), 7.04 (d, J=8.4Hz, 2H), 7.21 (d, J=8.4Hz, 2H), 7.51 (d, J=2.5Hz, 1H), 7.53 (d, J=2.5Hz, 1H)

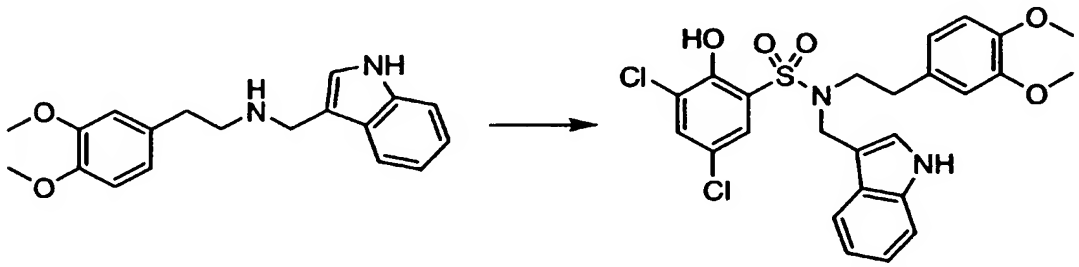
MS (EI)E/Z451 (M), 453 (M+2), 455 (M+4)

Preparation Example 159

Synthesis of

3,5-dichloro-N-[2-(3,4-dimethoxyphenyl)ethyl]-2-hydroxy-N-(indole-3-ylmethyl) benzenesulfonamide

The title compound (BAK-KA425) was obtained in the same manner as in Preparation Example 114.



BAK-KA425

^{1}H-NMR($CDCl_3$)δ:

2.67 (t, J=7.3Hz, 2H), 3.45 (t, J=7.3Hz, 2H), 3.78 (s, 3H), 3.83 (s, 3H), 6.44 (d, J=1.9Hz, 1H), 6.53 (dd, J=1.9, 8.1Hz, 1H), 6.71 (d, J=8.1Hz, 1H), 7.10-7.41 (m, 7H), 8.16 (brs, 1H), 9.27 (brs, 1H)

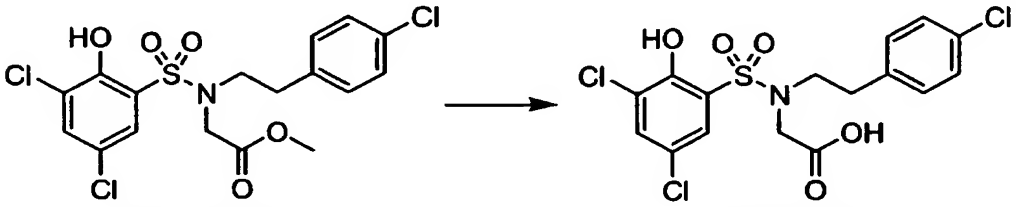
MS(EI)E/Z534(M), 536(M+2)

Preparation Example 160

Synthesis of

[[2-(4-chlorophenyl)ethyl][(3,5-dichloro-2-hydroxyphenyl)sulfonyl]amino]acetic acid

The title compound (BAK-KA426) was obtained in the same manner as in Preparation Example 116.



BAK-KA424 BAK-KA426

^{1}H-NMR($CDCl_3$)δ:

2.83 (t, J=7.2Hz, 2H), 3.51 (t, J=7.2Hz, 2H), 4.11 (s, 2H),

7.03 (d, J=8.4Hz, 2H), 7.23 (d, J=8.4Hz, 2H), 7.51 (d, J=2.5Hz, 1H),

7.53 (d, J=2.5Hz, 1H)

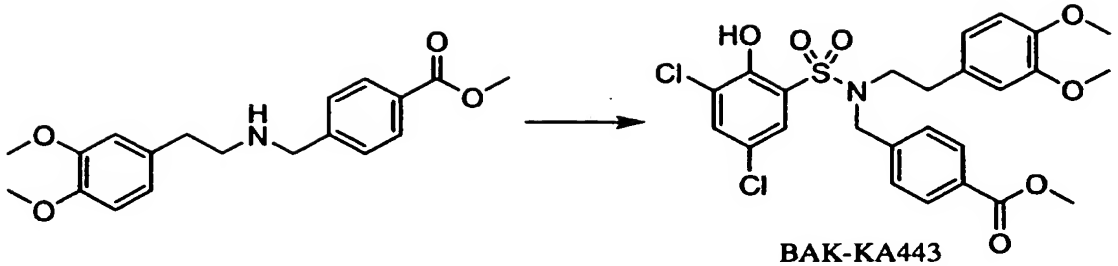
MS(EI)E/Z437(M),439(M+2),441(M+4)

Preparation Example 161

Synthesis of methyl

4-[[[(3,5-dichloro-2-hydroxyphenyl)sulfonyl][2-(3,4-dimethoxyphenyl)ethyl]amino] methyl]benzoate

The title compound (BAK-KA443) was obtained in the same manner as in Preparation Example 114.



BAK-KA443

^{1}H-NMR($CDCl_3$)δ:

2.61 (t, J=7.2Hz, 2H), 3.39 (t, J=7.2Hz, 2H), 3.81 (s, 3H), 3.84 (s, 3H), 3.93 (s, 3H), 4.45 (s, 2H), 6.45-6.74 (m, 3H), 7.33 (t, J=8.3Hz, 2H), 7.44 (d, J=2.5Hz, 1H), 7.54 (d, J=2.5Hz, 1H), 8.01 (t, J=8.3Hz, 2H), 9.04 (s, 1H)

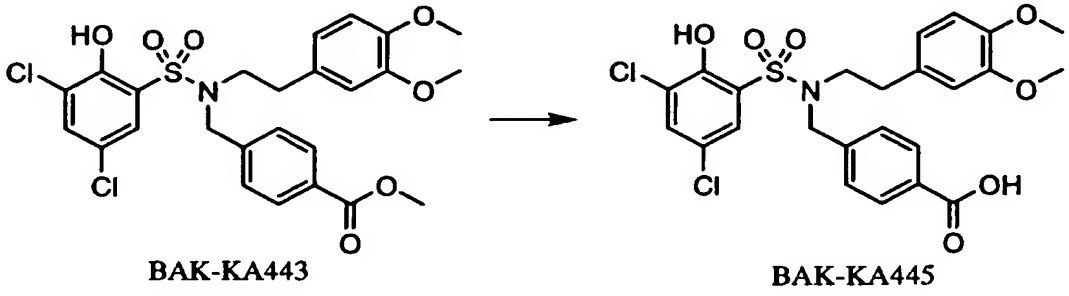
MS(EI)E/Z553(M),555(M+2),557(M+4)

Preparation Example 162

Synthesis of

4-[[[(3,5-dichloro-2-hydroxyphenyl)sulfonyl][2-(3,4-dimethoxyphenyl)ethyl]amino] methyl]benzoic acid

The title compound (BAK-KA445) was obtained in the same manner as in Preparation Example 116.



BAK-KA443 BAK-KA445

^{1}H-NMR($CDCl_3$)δ:

2.64 (t, J=7.0Hz, 2H), 3.42 (t, J=7.0Hz, 2H), 3.81 (s, 3H), 3.84 (s, 3H), 4.47 (s, 2H), 6.46-6.75 (m, 3H), 7.37 (t, J=8.0Hz, 2H), 7.44 (d, J=2.4Hz, 1H),

7.54 (d, J=2.4Hz, 1H), 8.07 (t, J=8.0Hz, 2H), 9.00 (brs, 1H)

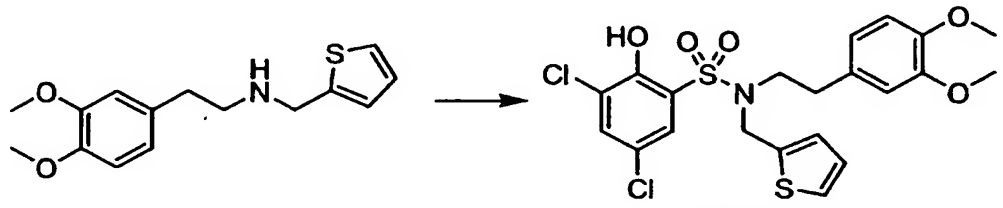
MS(EI)E/Z539(M),541(M+2),543(M+4)

Preparation Example 163

Synthesis of

3,5-dichloro-N-[2-(3,4-dimethoxyphenyl)ethyl]-2-hydroxy-N-[(2-thienyl)methyl] benzenesulfonamide

The title compound (BAK-KA450) was obtained in the same manner as in Preparation Example 114.



BAK-KA450

^{1}H-NMR($CDCl_3$)δ:

2.75 (t, J=7.2Hz, 2H), 3.44 (t, J=7.2Hz, 2H), 3.85 (s, 6H), 4.57 (s, 2H),

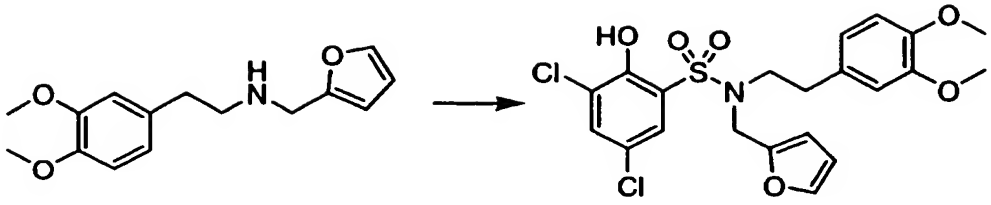
6.57-7.29 (m, 6H), 7.36 (d, J=2.5Hz, 1H), 7.51 (d, J=2.5Hz, 1H), 9.12 (s, 1H)

MS(EI)E/Z501(M^+),503(M+2),505(M+4)

Preparation Example 164

Synthesis of 3,5-dichloro-N-[2-(3,4-dimethylphenyl)ethyl]-N-[(2-furyl)methyl]-2-hydroxybenzenesulfonamide

The title compound (BAK-KA451) was obtained in the same manner as in Preparation Example 114.



BAK-KA451

^{1}H-NMR($CDCl_3$)δ:

2.79 (t, J=7.2Hz, 2H), 3.42 (t, J=7.2Hz, 2H), 3.86 (s, 3H), 3.87 (s, 3H), 4.40 (s, 2H), 6.24-6.81 (m, 6H), 7.34 (d, J=2.5Hz, 1H), 7.48 (d, J=2.5Hz, 1H), 9.21 (s, 1H)

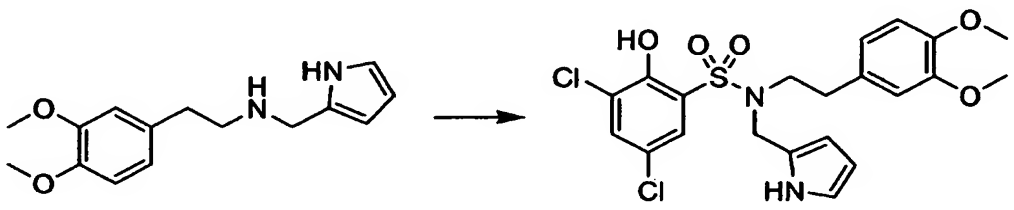
MS(EI)E/Z485(M),487(M+2),489(M+4)

Preparation Example 165

Synthesis of

3,5-dichloro-N-[2-(3,4-dimethylphenyl)ethyl]-2-hydroxy-N-(pyrrole-2-ylmethyl) benzenesulfonamide

The title compound (BAK-KA452) was obtained in the same manner as in Preparation Example 114.



BAK-KA452

^{1}H-NMR($CDCl_3$)δ:

2.63 (t, J=7.1Hz, 2H), 3.40 (t, J=7.1Hz, 2H), 3.83 (s, 3H), 3.85 (s, 3H), 4.34 (s, 2H), 6.12-6.83 (m, 6H), 7.32 (d, J=2.5Hz, 1H), 7.52 (d, J=2.5Hz, 1H), 8.58 (brs, 1H), 8.96 (s, 1H)

MS(EI)E/Z484(M^+),486(M+2),488(M+4)

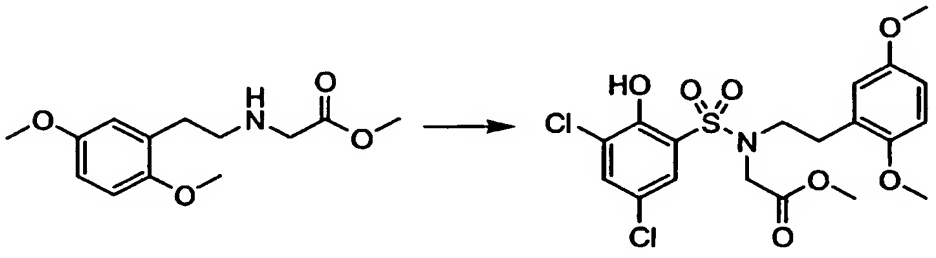
Preparation Example 166

Synthesis of methyl

[[(3,5-dichloro-2-hydroxyphenyl)sulfonyl][2-(2,5-dimethoxyphenyl)ethyl]

amino]acetate

The title compound (BAK-KA456) was obtained in the same manner as in Preparation Example 114.



BAK-KA456

^{1}H-NMR($CDCl_3$)δ:

2.79 (t, J=7.0Hz, 2H), 3.47 (t, J=7.0Hz, 2H), 3.73 (s, 6H), 3.75 (s, 3H), 4.14 (s, 2H), 6.60-6.70 (m, 3H), 7.50 (d, J=2.5Hz, 1H), 7.54 (d, J=2.5Hz, 1H), 9.14 (s, 1H)

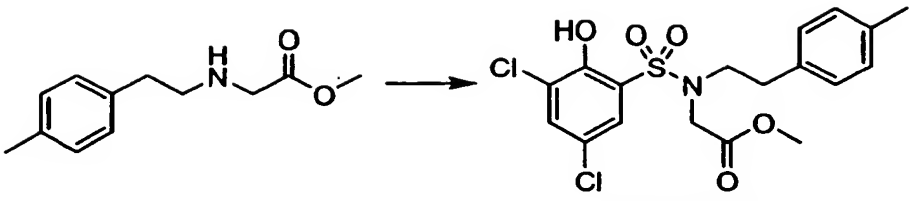
MS(EI)E/Z477(M),479(M+2)

Preparation Example 167

Synthesis of methyl

[[(3,5-dichloro-2-hydroxyphenyl)sulfonyl][2-(4-methylphenyl)ethyl]amino]acetate

The title compound (BAK-KA457) was obtained in the same manner as in Preparation Example 114.



BAK-KA457

^{1}H-NMR($CDCl_3$)δ:

2.30 (s, 3H), 2.80 (t, J=7.0Hz, 2H), 3.49 (t, J=7.0Hz, 2H), 3.70 (s, 3H), 4.04 (s, 2H), 6.98 (d, J=8.0Hz, 2H), 7.07 (d, J=8.0Hz, 2H), 7.52 (s, 2H), 8.98 (s, 1H)

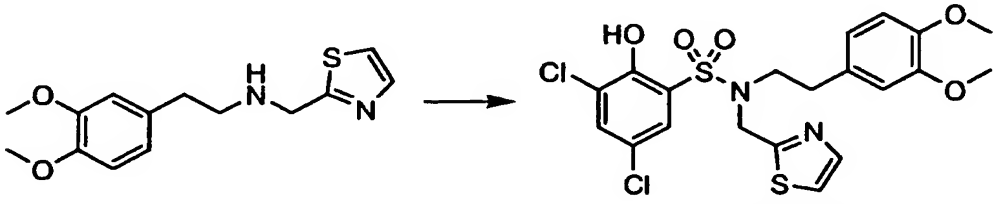
MS(EI)E/Z431(M)

Preparation Example 168

Synthesis of

3,5-dichloro-N-[2-(3,4-dimethoxyphenyl)ethyl]-2-hydroxy-N-[(1,3-thiazol-2-yl)methyl] benzenesulfonamide

The title compound (BAK-KA465) was obtained in the same manner as in Preparation Example 114.



BAK-KA465

^{1}H-NMR($CDCl_3$)δ:

2.77 (t, J=7.1Hz, 2H), 3.51 (t, J=7.2Hz, 2H), 3.84 (s, 3H), 3.85 (s, 3H), 4.78 (s, 2H), 6.57-6.76 (m, 3H), 7.36 (d, J=3.3Hz, 1H), 7.48 (d, J=2.6Hz, 1H), 7.51 (d, J=2.6Hz, 1H), 7.73 (d, J=3.3Hz, 1H)

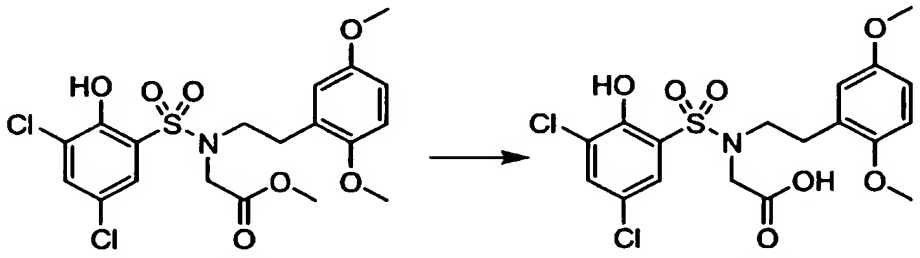
MS(EI)E/Z502(M),504(M+2)

Preparation Example 169

Synthesis of

[[(3,5-dichloro-2-hydroxyphenyl)sulfonyl][2-(2,5-dimethoxyphenyl)ethyl]amino]acetic acid

The title compound (BAK-KA459) was obtained in the same manner as in Preparation Example 116.



BAK-KA456 BAK-KA459

^{1}H-NMR($CDCl_3$)δ:

2.79 (t, J=7.0Hz, 2H), 3.49 (t, J=7.0Hz, 2H), 3.74 (s, 3H), 3.74 (s, 3H), 4.19 (s, 2H), 6.59-6.69 (m, 3H), 7.49 (d, J=2.5Hz, 1H), 7.53 (d, J=2.5Hz, 1H)

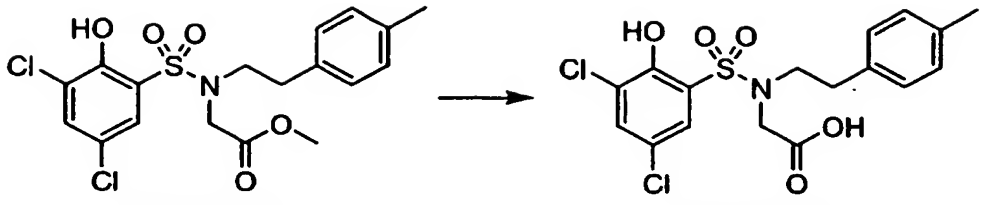
MS(EI)E/Z463(M),465(M+2)

Preparation Example 170

Synthesis of

[[(3,5-dichloro-2-hydroxyphenyl)sulfonyl][2-(4-methylphenyl)ethyl]amino]acetic acid

The title compound (BAK-KA460) was obtained in the same manner as in Preparation Example 116.



BAK-KA457 BAK-KA460

^{1}H-NMR($CDCl_3$)δ:

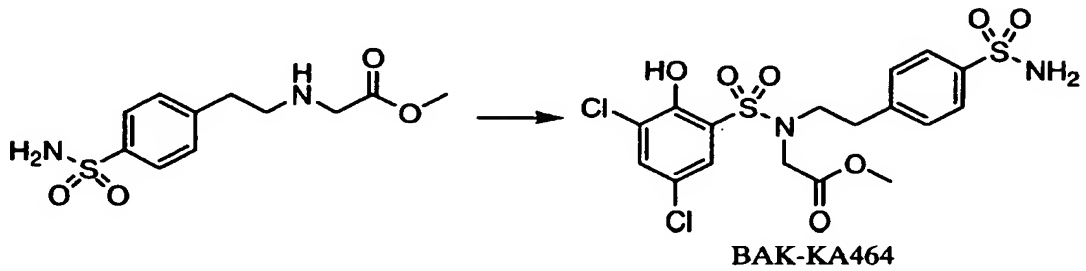
2.31 (s, 3H), 2.81 (t, J=7.2Hz, 2H), 3.50 (t, J=7.2Hz, 2H), 4.09 (s, 2H), 6.97 (d, J=8.1Hz, 2H), 7.06 (d, J=8.0Hz, 2H), 7.50 (d, J=2.5Hz, 1H), 7.52 (d, J=2.5Hz, 1H)

MS(EI)E/Z417(M)

Preparation Example 171

Synthesis of methyl [[2-[4-(aminosulfonyl)phenyl]ethyl][(3,5-dichloro-2-hydroxyphenyl)sulfonyl] amino]acetate

The title compound (BAK-KA464) was obtained in the same manner as in Preparation Example 114.



BAK-KA464

^{1}H-NMR($CDCl_3$)δ:

2.97 (t, J=7.1Hz, 2H), 3.54 (t, J=7.1Hz, 2H), 3.70 (s, 3H), 4.05 (s, 2H), 4.80 (brs, 2H), 7.30 (d, J=8.3Hz, 2H), 7.55 (s, 2H), 7.85 (d, J=8.3Hz, 2H), 8.81 (s, 1H)

MS(EI)E/Z496(M), 498(M+2)

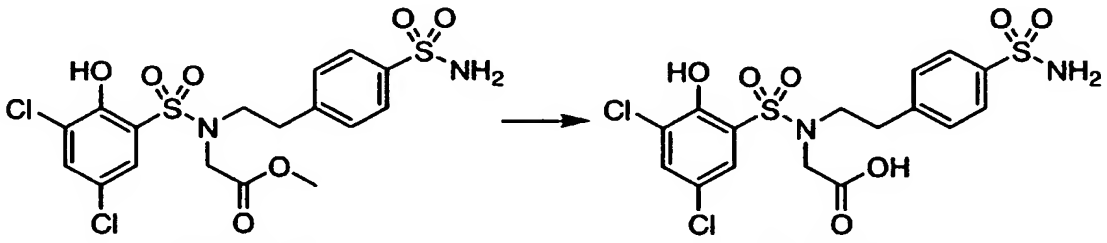
Preparation Example 172

Synthesis of

[[2-[4-(aminosulfonyl)phenyl]ethyl][(3,5-dichloro-2-hydroxyphenyl)sulfonyl]amino]

acetic acid

The title compound (BAK-KA466) was obtained in the same manner as in Preparation Example 116.



BAK-KA464 BAK-KA466

^{1}H-NMR($CDCl_3$)δ:

2.93 (t, J=7.1Hz, 2H), 3.54 (t, J=7.1Hz, 2H), 4.04 (s, 2H), 5.99 (s, 2H),

7.26 (d, J=8.3Hz, 2H), 7.52 (d, J=2.6Hz, 1H), 7.66 (d, J=2.6Hz, 1H),

7.83 (d, J=8.3Hz, 2H)

MS(Q-TOF)E/Z +ESI483.0(M),485(M)

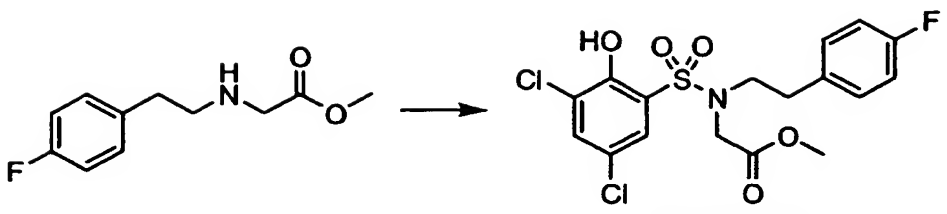
-ESI481.0(M-1),483.0(M+1)

Preparation Example 173

Synthesis of methyl

[[(3,5-dichloro-2-hydroxyphenyl)sulfonyl][2-(4-fluorophenyl)ethyl]amino]acetate

The title compound (BAK-KA469) was obtained in the same manner as in Preparation Example 114.



BAK-KA469

^{1}H-NMR($CDCl_3$)δ:

2.84 (t, J=7.2Hz, 2H), 3.00 (t, J=7.2Hz, 2H), 3.70 (s, 3H), 4.03 (s, 2H),

6.91-7.12 (m, 4H), 7.53 (s, 2H), 8.92 (s, 1H)

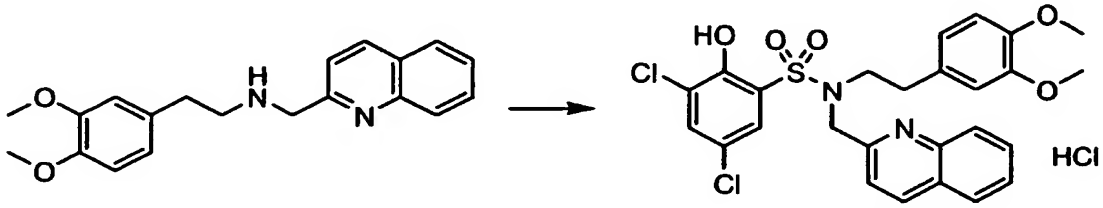
MS(EI)E/Z435(M)

Preparation Example 174

Synthesis of

3,5-dichloro-N-[2-(3,4-dimethylphenyl)ethyl]-2-hydroxy-N-(quinolin-2-ylmethyl) benzenesulfonamide hydrochloride

The title compound (BAK-KA470) was obtained in the same manner as in Preparation Example 114.



BAK-KA470

^{1}H-NMR($CDCl_3$)δ:

2.80 (t, J=7.0Hz, 2H), 3.64 (t, J=7.0Hz, 2H), 3.68 (s, 3H), 3.71 (s, 3H),

5.53 (s, 2H), 6.41-6.63 (m, 3H), 7.58 (d, J=2.5Hz, 1H), 7.72 (d, J=2.5Hz, 1H),

7.89-7.94 (m, 2H), 8.03-8.10 (m, 2H), 8.59 (d, 1H), 8.83 (d, 1H)

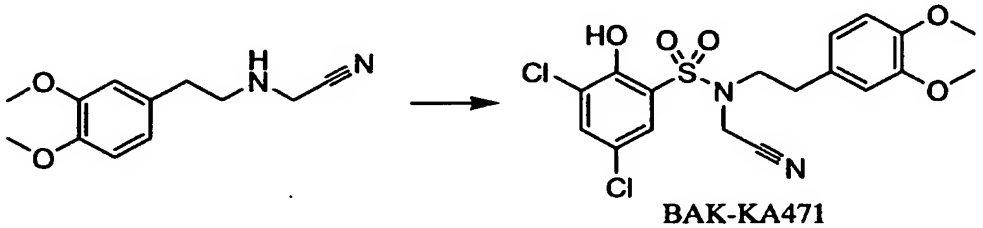
MS(Q-TOF)E/Z +ESI545.1(M-HCl+1)

-ESI546.1(M-HCl-1)

Preparation Example 175

Synthesis of 3,5-dichloro-N-(cyanomethyl)-N-[2-(3,4-dimethoxyphenyl)ethyl]-2-hydroxybenzenesulfonamide

The title compound (BAK-KA471) was obtained in the same manner as in Preparation Example 114.



BAK-KA471

^{1}H-NMR($CDCl_3$)δ:

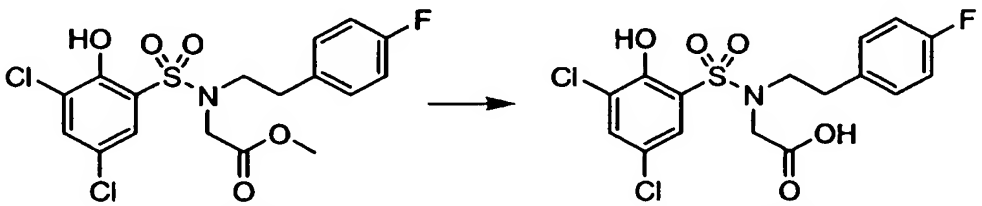
2.88 (t, J=7.0Hz, 2H), 3.55 (t, J=7.0Hz, 2H), 3.87 (s, 2H), 4.15 (s, 2H), 6.68-6.81 (m, 3H), 7.56 (d, J=2.5Hz, 1H), 7.58 (d, J=2.5Hz, 1H), 8.10 (brs, 1H)

MS(EI)E/Z444(M),446(M+2)

Preparation Example 176

Synthesis of [[(3,5-dichloro-2-hydroxyphenyl)sulfonyl][2-(4-fluorophenyl)ethyl]amino]acetic acid

The title compound (BAK-KA472) was obtained in the same manner as in Preparation Example 116.



BAK-KA469 BAK-KA472

^{1}H-NMR($CDCl_3$)δ:

2.83 (t, J=7.2Hz, 2H), 3.49 (t, J=7.2Hz, 2H), 4.10 (s, 2H), 6.91-7.11 (m, 4H), 7.52 (s, 2H)

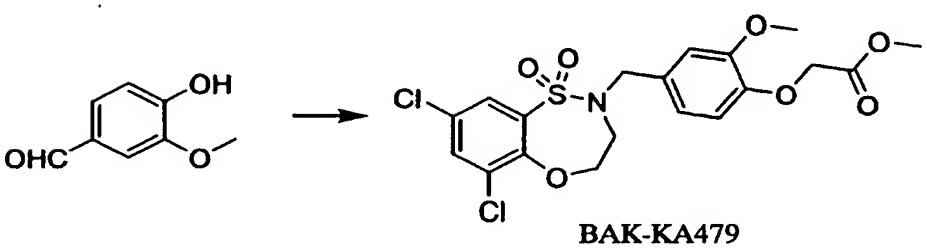
MS(EI)E/Z421(M), 423(M+2)

Preparation Example 177

Synthesis of

6,8-dichloro-2-[3-methoxy-4-[(methoxycarbonyl)methoxy]benzyl]-3,4-dihydro-2H-5,1,2-benzoxazepine][2-(4-fluorophenyl)ethyl]amino]acetic acid

The title compound (BAK-KA479) was obtained in the same manner as in Preparation Example 142.



BAK-KA479

^{1}H-NMR($CDCl_3$)δ:

3.66 (t, J=4.3Hz, 2H), 3.79 (s, 3H), 3.87 (s, 3H), 4.16 (s, 2H), 4.21 (t, J=4.3Hz, 2H), 4.69 (s, 2H), 6.74-6.89 (m, 3H), 7.59 (d, J=2.5Hz, 1H), 7.78 (d, J=2.5Hz, 1H)

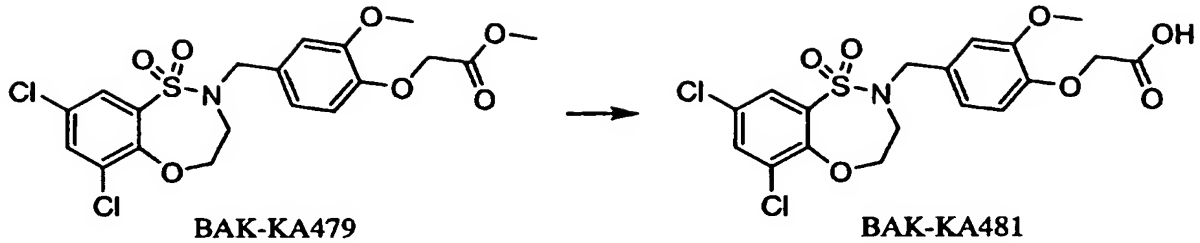
MS(EI)E/Z475(M),477(M+2)

Preparation Example 178

Synthesis of

2-[4-(carboxymethoxy)-3-methoxybenzyl]-6,8-dichloro-3,4-dihydro-2H-5,1,2-benzoxazepine-1,1-dioxide

The title compound (BAK-KA481) was obtained in the same manner as in Preparation Example 68.



BAK-KA479 BAK-KA481

^{1}H-NMR($CDCl_3$)δ:

3.67 (t, J=4.2Hz, 2H), 3.90 (s, 3H), 4.17 (s, 2H), 4.24 (t, J=4.2Hz, 2H),

4.68 (s, 2H), 6.79-6.94 (m, 3H), 7.60 (d, J=2.5Hz, 1H), 7.78 (d, J=2.5Hz, 1H)

MS(EI)E/Z461(M),463(M+2)

Test Example 1

Verification of antitussive effect in capsaicin induced cough model (1):

Hartley guinea pigs (Tokyo Laboratory Animal Science Co., Ltd., male, five-weeks of age) were placed in the cylinder of a body-plethysmograph and exposed to physiological saline solution of capsaicin for 7-10 minutes with an ultrasonic nebulizer connected to the front of the cylinder to induce coughing. Change in the internal pressure of the body plethysmograph was recorded using a polygraph, and while simultaneously monitoring change in the polygraph reading and movement of the animal's chest, the number of coughs were measured.

The number of coughs generated before administration of the test compound (pre-value) and the number of coughs generated one hour after administration of the test compound (post-value) were used to calculate the cough suppression rate in accordance with the following formula.

Cough suppression rate (%) = (pre-value - post-value)/pre-value × 100

Furthermore, to determine if the antitussive effect of the test compound was central or peripheral, methysergide (3mg/kg) was intraperitoneally administered 15 minutes before administration of the test compound and the antitussive effect of the test

compound was examined.

Since it is known that the manifestation of the central antitussive effect involves the activation of the serotonin receptor (5-HT1A) of the postsynaptic membrane (Nippon Yakurigaku Zasshi, 111 (6), p345 (1998)), and that methysergide, which is a serotonin-receptor antagonist, causes the central antitussive effect to disappear or reduce, a central or peripheral effect can be determined by the presence or absence of the influence of methysergide on the antitussive effect of test compounds.

(Results)

Table 1

Test compound (30 mg/kg)	Cough suppression rate (A)	Pretreatment with methysergide		Action mechanism
		Cough suppression rate (B)	Residual ratio of antitussive effect (%)	
Preparation Example 2	56.7	nt	-	-
Preparation Example 3	69.6	68.8	98.9	Peripheral
Preparation Example 34	63.0	nt	-	-
Moguisteine	59.5	67.0	112.6	Peripheral

Residual ratio (%) = cough suppression rate (B)/cough suppression rate (B) × 100

Three types of test compounds (Preparation Examples 2, 3, and 34) showed an antitussive effect after oral administration at a dosage of 30mg/kg.

Furthermore, the compound of Preparation Example 3 showed an antitussive effect in the guinea pig pretreated with methysergide (the residual ratio of the antitussive effect was 98.9%). Therefore, a possibility of having the same peripheral antitussive effect as moguisteine was shown.

Test Example 2

Verification of antitussive effect in capsaicin induced cough model (2):

Using the method of Test Example 1, the antitussive effect of a test compound at a dosage of 10 mg/kg was examined. In regard to the action mechanism, test compounds

having an antitussive effect with a residual ratio of 70% or more in the guinea pig pretreated with methysergide were judged to possess a peripheral antitussive effect. Dihydrocodeine, which is a central antitussive, was used as a control.

(Results)

Table 2

Test compound (10 mg/kg)	Cough suppression rate (%)	Pretreatment with methysergide	
		Residual ratio of antitussive effect (%)	Action mechanism
Preparation Example 102	69.2	nt	-
Preparation Example 22	53.5	nt	-
Preparation Example 48	67.6	121.4	Peripheral
Preparation Example 47	86.5	77.7	Peripheral
Preparation Example 49	56.0	94.2	Peripheral
Preparation Example 52	71.5	98.9	Peripheral
Preparation Example 54	62.7	102.1	Peripheral
Preparation Example 55	44.5	nt	-
Preparation Example 59	65.7	99.1	Peripheral
Preparation Example 79	69.8	87.2	Peripheral
Preparation Example 80	63.3	80.6	Peripheral
Preparation Example 93	82.1	86.5	Peripheral
Preparation Example 94	74.6	70.2	Peripheral
Preparation Example 83	76.4	nt	-
Preparation Example 85	83.5	75.8	Peripheral
Preparation Example 87	71.5	nt	-
Preparation Example 97	66.5	34.9	Central
Preparation Example 99	66.8	80.1	Peripheral
Preparation Example 72	71.3	51.6	Central
Preparation Example 68	64.4	nt	-
Preparation Example 77	62.8	93.8	Peripheral
Preparation Example 116	46.9	nt	-
Preparation Example 117	68.8	76.7	Peripheral
Preparation Example 119	61.9	69.5	Central
Preparation Example 120	64.5	nt	-
Preparation Example 125	62.2	65.9	Central
Preparation Example 127	82.1	72.4	Peripheral
Preparation Example 129	73.3	67.9	Central
Preparation Example 132	67.6	nt	-
Preparation Example 136	71.9	nt	-
Dihydrocodeine	65.6	24.5	Central
Control (vehicle)	28.7	-	-

Almost every test compound possessed an antitussive effect equal to or more

than that of dihydrocodeine when administered orally at a dosage of 10 mg/kg. Furthermore, nearly half (15 compounds) of the tested compounds showed a possibility of possessing a peripheral antitussive effect.

Test Example 3

Verification of antitussive effect in capsaicin induced cough model (3):

Using the method of Test Example 1, the antitussive effect of a test compound at a dosage of 3 mg/kg was examined.

Dihydrocodeine, which is a central antitussive, was used as a control.

(Results)

Table 3

Test compound (3 mg/kg)	Cough suppression rate (%)
Preparation Example 48	59.6
Preparation Example 47	57.8
Preparation Example 52	77.5
Preparation Example 54	56.4
Preparation Example 93	62.7
Preparation Example 94	57.5
Preparation Example 85	59.1
Dihydrocodeine	52.4
Control (vehicle)	28.7

Seven test compounds which showed a peripheral antitussive effect in Test Example 2 possessed an antitussive effect equal to or more than that of dihydrocodeine when administered orally at a dosage of 3mg/kg.

INDUSTRIAL APPLICABILITY

The compound of the present invention possesses an outstanding antitussive effect and also a peripheral antitussive effect. Therefore, these compounds have an action mechanism different from that of existing central antitussives, and can be used as an outstanding antitussive without causing most of the side effects caused by central

antitussives.

The antitussive of the present invention comprising this compound as an active component can be effectively used in the suppression and relief of coughing accompanying many diseases, for example, respiratory ailments such as influenza, bronchitis, pneumonia, asthma, upper respiratory inflammation, pleurisy, and whooping cough.